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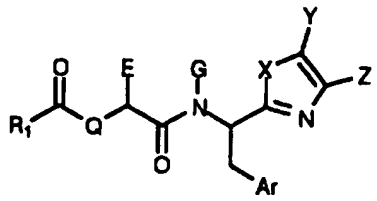
(54) Title: ENDOTHELIN ANTAGONISTS

(57) Abstract

A compound of formula (I), or a pharmaceutically acceptable salt thereof, as well as processes for and intermediates in the preparation thereof, and methods and compositions for antagonizing endothelin.



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US Priority #'s

US 19940322114

1994 1012

19950442124

ENDOTHELIN A

No - von, 927, WO, endothelin in 082

This is a continuation-in-part of U.S. 08/322,114, filed August 18, 1994.

Cite to US-A case!

Technical Field

The present invention relates to com antagonists, processes for making such co employed in these processes and methods endothelin.

Background of the Invention

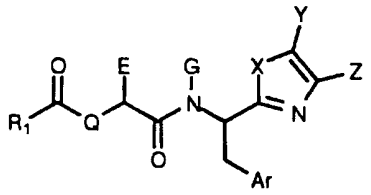
Endothelin (ET) is a 21 amino acid p endothelial cells. ET is produced by enzymatic cleavage of a Trp-Val bond in the precursor peptide big endothelin (Big ET). This cleavage is caused by an endothelin converting enzyme (ECE). Endothelin has been shown to constrict arteries and veins, increase mean arterial blood pressure, decrease cardiac output, increase cardiac contractility in vitro, stimulate mitogenesis in vascular smooth muscle cells in vitro, contract non-vascular smooth muscle including guinea pig trachea, human urinary bladder strips and rat uterus in vitro, increase airway resistance in vivo, induce formation of gastric ulcers, stimulate release of atrial natriuretic factor in vitro and in vivo, increase plasma levels of vasopressin, aldosterone and catecholamines, inhibit release of renin in vitro and stimulate release of gonadotropins in vitro.

It has been shown that vasoconstriction is caused by binding of endothelin to its receptors on vascular smooth muscle (Nature 332 411 (1988), FEBS Letters 231 440 (1988) and Biochem. Biophys. Res. Commun. 154 868

(1988)). An agent which suppresses endothelin production or an agent which binds to endothelin or which inhibits the binding of endothelin to an endothelin receptor will produce beneficial effects in a variety of therapeutic areas. In fact, an anti-endothelin antibody has been shown, upon intrarenal infusion, to ameliorate the adverse effects of renal ischemia on renal vascular resistance and glomerular filtration rate (Kon, et al., J. Clin. Invest. 83 1762 (1989)). In addition, an anti-endothelin antibody attenuated the nephrotoxic effects of intravenously administered cyclosporin (Kon, et al., Kidney Int. 37 1487 (1990)) and attenuated infarct size in a coronary artery ligation-induced myocardial infarction model (Watanabe, et al., Nature 344 114 (1990)).

Disclosure of the Invention

In accordance with the present invention there are compounds of the formula (I):



(I)

wherein

X is -N(R_2)-, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;

Q is -O- or -CR_3R_4- wherein R_3 and R_4 are independently selected from hydrogen, loweralkyl, cycloalkyl and cycloalkylalkyl;

R_1 is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, arylalkenyl, aryl, alkoxy, arylalkoxy, cycloalkoxy, cycloalkylalkoxy, hydroxyarylalkyl, aryloxy, alkylamino, (cycloalkyl)amino, arylamino, (cycloalkylalkyl)amino, (arylalkyl)amino, dialkylamino, diarylamino, (alkyl)(cycloalkyl)amino, (alkyl)(aryl)amino,

(alkyl)(cycloalkylalkyl)amino, (alkyl)(arylalkyl)amino, heterocyclic, (heterocyclic)alkyl, (heterocyclic)amino, (heterocyclic)(alkyl)amino, (heterocyclicalkyl)amino, (heterocyclicalkyl)(alkyl)amino, spirocarbocyclic or spiroheterocyclic;

E is loweralkyl optionally substituted with one, two or three substituents independently selected from cyano, halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy and azido;

G is hydrogen or loweralkyl;

Ar is bicyclic aryl, bicyclic heteroaryl or aryl;

Y is selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl; and

(7) arylalkyl; and

Z is selected from the group consisting of

(1) -C(O)-W wherein W is -OR_{10} wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) -V wherein V is

(a) -$S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or aryl,

(b) -PO_3H_2,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

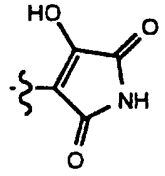
(h) tetrazolyl,

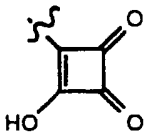
(i) hydroxy,

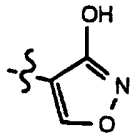
(j) alkoxy,

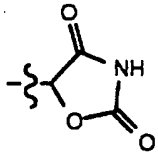
(k) sulfonamido,

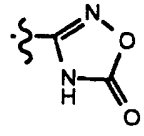
(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is defined as above,

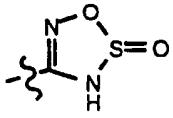
(m)  ,

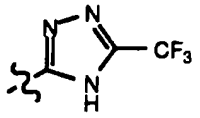
(n)  ,

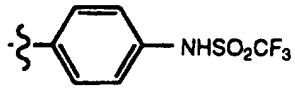
(o)  ,

(p)  ,

(q)  ,

(r)  ,

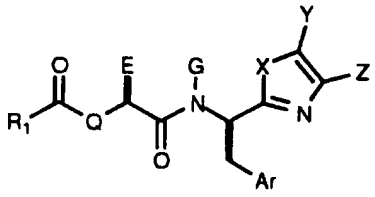
(s)  , or

(t)  ; and

(3) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the present invention is a compound of formula (II):



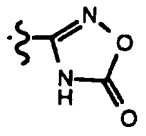
(II)

wherein R_1, Q, E, Ar, G, Ar, X, Y and Z are as defined above;
or a pharmaceutically acceptable salt thereof.

A more preferred embodiment of the present invention is a compound of formula (I) or (II) wherein
Z is

(1) $-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) -(tetrazolyl),



(3) or

(4) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl, haloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

Another more preferred embodiment of the present invention is a compound of formula (I) or (II)

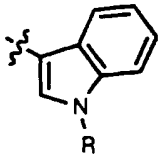
wherein

R_1 is loweralkyl, (alkyl)(cycloalkyl)amino, cycloalkoxy, arylamino, (alkyl)(aryl)amino, diarylamino, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkoxy, (cycloalkylalkyl)amino, (cycloalkyl)amino, alkoxy, (arylalkyl)amino, dialkylamino, spiroheterocyclic or heterocyclic;

Q is -O- or $-CH(R_4)-$ wherein R_4 is hydrogen or loweralkyl;

E is isobutyl;

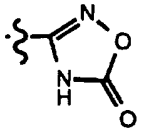
G is hydrogen;

Ar is  wherein R is hydrogen, loweralkyl or alkanoyl;

Y is hydrogen, arylalkyl, haloalkyl, loweralkyl, aryl or cycloalkyl;

Z is (1) -CO-W, wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group,

(2) -(tetrazolyl),



(3) or

(4) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl, haloalkyl or aryl;

and

X is $-N(R_2)-$ or -O- wherein R_2 is hydrogen or loweralkyl;

or a pharmaceutically acceptable salt thereof.

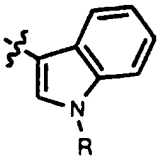
An even more preferred embodiment is a compound of formula (I) or (II) wherein

R_1 is (cycloalkyl)amino, arylamino, aryl, arylalkyl, spiroheterocyclic, heterocyclic, (alkyl)(aryl)amino, cycloalkoxy, cycloalkylalkyl or (alkyl)(cycloalkyl)amino;

Q is -O- or $-CH_2-$;

E is isobutyl;

G is hydrogen;



Ar is wherein R is loweralkyl;

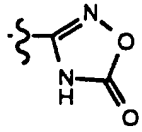
X is -NH- or -O-,

Y is loweralkyl; and

Z is

(1) $-CO_2H$,

(2) -(tetrazolyl),



(3) or

(4) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl or aryl;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to processes for preparing the compounds of formula (I) and (II) and to the synthetic intermediates employed in these processes.

The present invention also relates to a method of antagonizing endothelin in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of formula (I) or (II).

The invention further relates to endothelin antagonizing compositions comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of formula (I) or (II).

The compounds of the invention comprise two or more asymmetrically substituted carbon atoms. As a result, all stereoisomers (for example, racemic mixtures, mixtures of diastereomers, as well as single diastereomers) of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13 - 30.

The terms "Gly", "Trp", "Val" and "Leu" as used herein refer to glycine, tryptophan, valine and leucine, respectively. In general, the amino acid abbreviations used herein follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides (Eur. J. Biochem. 1984, 158, 9-31).

The term "naturally occuring amino acid" refers to an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. The stereochemistry at the asymmetric center can be of the D- or L- configuration.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl,

4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "carboxy protecting group" as used herein refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* , for example by enzymatic hydrolysis, to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields,

as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C_1 to C_8 loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); haloalkyl; alkenyl; cycloalkyl and substituted derivatives thereof such as cyclohexyl, cylcopentyl and the like; cycloalkylalkyl and substituted derivatives thereof such as cyclohexylmethyl, cylcopentylmethyl and the like; arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxyl)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-

dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

The terms "loweralkyl" or "alkyl" as used herein refer to straight or branched chain alkyl radicals containing from 1 to 10 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkylamino" as used herein refers to $R_{51}NH$- wherein R_{51} is a loweralkyl group, for example, ethylamino, butylamino, and the like.

The term "alkylaminocarbonyl" as used herein refers to an alkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl and the like.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to R_{90}-C(O)-NH-R_{91}- wherein R_{90} is an alkylamino group and R_{91} is an alkylene group. Examples of alkylaminocarbonylaminoalkyl include methylaminocarbonylaminomethyl, ethylaminocarbonylaminomethyl and the like.

The term "dialkylamino" as used herein refers to $R_{56}R_{57}N$- wherein R_{56} and R_{57} are independently selected from loweralkyl, for example diethylamino. methyl propylamino, and the like.

The term "dialkylaminoalkyl" as used herein refers to $R_{71}R_{72}N$-R_{73}- wherein R_{71} and R_{72} are independently selected from loweralkyl and R_{73} is an alkylene group. Examples of dialkylaminoalkyl include dimethylaminomethyl, dimethylaminoethyl, N-ethyl-N-methylaminomethyl, and the like.

The term "dialkylaminocarbonyl" as used herein refers to a dialkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of dialkylaminocarbonyl include dimethylaminocarbonyl, diethylaminocarbonyl and the like.

The term "dialkylaminocarbonylalkyl" as used herein refers to R_{100}-C(O)-R_{101}- wherein R_{100} is a dialkylamino group and R_{101} is an alkylene group, for example, dimethylaminocarbonylmethyl and the like.

The term "(alkyl)arylamino" as used herein refers to $R_{60}R_{61}N$- wherein R_{60} is an aryl group and R_{61} is a loweralkyl group.

The term "(alkyl)(arylalkyl)amino" as used herein refers to $R_{64}R_{65}N$- wherein R_{64} is an arylalkyl group and R_{65} is a loweralkyl group.

The term "(alkyl)(cycloalkyl)amino" as used herein refers to $R_{58}R_{59}N$- wherein R_{58} is a cycloalkyl group and R_{59} is a loweralkyl group.

The term "(alkyl)(cycloalkylalkyl)amino" as used herein refers to $R_{62}R_{63}N$- wherein R_{62} is an cycloalkylalkyl group and R_{63} is a loweralkyl group.

The term "alkanoyl" as used herein refers to an alkyl group as previously defined appended to the parent molecular moiety through a carbonyl (-C(O)-) group. Examples of alkanoyl include acetyl, propionyl and the like.

The term "alkanoylaminoalkyl" as used herein refers to R_{93}-NH-R_{94}- wherein R_{93} is an alkanoyl group and R_{94} is an alkylene group. Examples of alkanoylaminoalkyl include acetylaminomethyl, acetylaminoethyl and the like.

The term "alkanoyloxyalkyl" as used herein refers to R_{74}-O-R_{75}- wherein R_{74} is an alkanoyl group and R_{75} is an alkylene group. Examples of alkanoyloxyalkyl include acetoxymethyl, acetoxyethyl and the like.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon radical containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Alkenyl groups include, for example, vinyl (ethenyl), allyl (propenyl), butenyl, 1-methyl-2-buten-1-yl and the like.

The term "alkoxy" as used herein refers to $R_{41}O$- wherein R_{41} is a loweralkyl group, as defined above. Examples of alkoxy include, but are not limited to, ethoxy, tert-butoxy, and the like.

The term "alkoxyalkoxy" as used herein refers to $R_{80}O$-$R_{81}O$- wherein R_{80} is loweralkyl as defined above and R_{81} is alkylene. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like.

The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like.

The term "alkoxycarbonylaminoalkyl" as used herein refers to R_{88}-C(O)-NH-R_{89}- wherein R_{88} is an alkoxy group and R_{89} is an alkylene group.

The term "alkoxycarbonylalkyl" as used herein refers to R_{84}-C(O)-R_{85}- wherein R_{84} is an alkoxy group and R_{85} is an alkylene group. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, methoxcarbonylethyl, ethoxycarbonylmethyl and the like.

The term "alkoxycarbonyloxyalkyl" as used herein refers to R_{86}-C(O)-O-R_{87}- wherein R_{86} is an alkoxy group and R_{87} is an alkylene group. Examples of alkoxycarbonyloxyalkyl include tert-butyloxycarbonyloxymethyl, tert-butyloxycarbonyloxyethyl, and the like.

The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$ and the like.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or more aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. The term "bicyclic aryl" as used herein includes naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group, for example, phenylethenyl (cinnamyl) and the like.

The term "arylalkoxy" as used herein refers to $R_{42}O$- wherein R_{42} is an arylalkyl group, for example, benzyloxy, and the like.

The term "arylalkyl" as used herein refers to an aryl group as previously defined, appended to a loweralkyl radical, for example, benzyl and the like.

The term "arylalkylamino" as used herein refers to $R_{55}NH$- wherein R_{55} is an arylalkyl group, for example benzylamino and the like.

The term "arylamino" as used herein refers to $R_{53}NH$- wherein R_{53} is an aryl group, for example, anilino, and the like.

The term "aryloxy" as used herein refers to $R_{45}O$- wherein R_{45} is an aryl group, for example, phenoxy, and the like.

The term "aroyloxyalkyl" as used herein refers to R_{82}-C(O)-O-R_{83}- wherein R_{82} is an aryl group and R_{83} is an alkylene group. Examples of aroyloxyalkyl include benzoyloxymethyl, benzoyloxyethyl and the like.

The term "cycloalkyl" as used herein refers to an carbocyclic ring system having 3 to 10 carbon atoms and 1 to 3 rings including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl, and the like. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, aryl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkoxy" as used herein refers to $R_{43}O$- wherein R_{43} is a cycloalkyl group, for example, cyclohexyloxy, and the like.

The term "cycloalkylalkoxy" as used herein refers to $R_{44}O$- wherein R_{44} is a cycloalkylalkyl group, for example, cyclohexylmethoxy, and the like.

The term "(cycloalkyl)amino" as used herein refers to $R_{52}NH$- wherein R_{52} is a cycloalkyl group, for example, cyclohexylamino, and the like.

The term "(cycloalkylalkyl)amino" as used herein refers to $R_{54}NH$- wherein R_{54} is a cycloalkylalkyl group, for example, cyclohexylmethylamino, and the like.

The term "diarylamino" as used herein refers to $R_{30}R_{31}N$- wherein R_{30} and R_{31} are independently selected from aryl as defined above.

The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

The terms "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected

from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; or two sulfur atoms in non-adjacent positions. As used herein "heterocyclic" also includes 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,5-oxadiazole, 1,3,5-thiadiazole and tetrazole. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered ring have 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, decahydroquinolyl, tetrahydoisoquinolinyl, indolinyl, benzofuryl or benzothienyl, imidazopyridyl, pyrrolopyridyl and the like). The term "heterocyclic" also includes tricyclic groups in which any of the above heterocyclic rings is fused to two benzene rings or two cyclohexane rings or two other heterocyclic rings (for example, carbazolyl, iminodibenzyl and the like). Heterocyclics include: azirdinyl, azetidinyl, benzimidazolyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzoxazolyl, benzothiazolyl, benzothienyl, carbazolyl, dihydropyranyl, dihydrofuranyl, dioxanyl, dioxolanyl, furyl, homopiperidinyl, imidazolyl, imidazolinyl, imidazolidinyl, imidazopyridyl, iminodibenzyl, indolinyl, indolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, thiomorpholinyl, naphthyridinyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolindinylpyridyl, pyrrolinyl, pyrrolopyridyl, pyrrolyl, quinolinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, thiazolyl, and thienyl.

Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, arylalkyl, -COOH, $-SO_3H$, alkanoyl and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above.

The term "(heterocyclic)amino" as used herein refers to $R_{35}NH$- wherein R_{35} is a heterocyclic group. Examples of (heterocyclic)amino include 4-pyridylamino, 3-pyridylamino, 2-pyridylamino and the like.

The term "(heterocyclic)(alkyl)amino" as used herein refers to $R_{35a}R_{35b}NH$- wherein R_{35a} is a heterocyclic group and $R35_b$ is a loweralkyl group. Examples of (heterocyclic)(alkyl)amino include (4-pyridyl)(methyl)amino, (3-pyridyl)(methyl)amino, (2-pyridyl)(methyl)amino and the like.

The term "(heterocyclicalkyl)amino" as used herein refers to $R_{35c}NH$- wherein R_{35c} is a heterocyclicalkyl group. Examples of (heterocyclic)amino include 4-pyridylmethylamino, 3-pyridylmethylamino, 2-pyridylmethylamino and the like.

The term "(heterocyclicalkyl)(alkyl)amino" as used herein refers to $R_{35d}R_{35e}NH$- wherein R_{35d} is a heterocyclicalkyl group and $R35_e$ is a loweralkyl group. Examples of (heterocyclicalkyl)(alkyl)amino include (4-pyridylmethyl)(methyl)amino, (3-pyridylmethyl)(methyl)amino, (2-pyridylmethyl)(methyl)amino and the like.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to R_{96}-C(O)-O-R_{97}- wherein R_{96} is a heterocyclic group and R_{97} is an alkylene group, for example, 4-methylpiperazinylcarbonyloxymethyl and the like.

The term "bicyclic heteroaryl" as used herein refers to a monocyclic heterocycle as defined above to which is fused a benzene ring, a cyclohexane ring or a monocyclic heterocycle as defined above, with the proviso that at least one of the rings of the bicyclic group is aromatic. Examples of bicyclic heteroaryl include indolyl, indolinyl, quinolyl, isoquinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzofuryl, benzothienyl and the like. Bicyclic heteroaryl groups can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, arylalkyl, -CHO, -COOH, -SO_3H

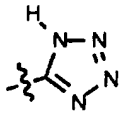
and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "hydroxyarylalkyl" as used herein refers to an arylalkyl radical to which is appended on the alkyl part an -OH group, for example, 2-hydroxy-1-pheneth-2-yl and the like.

The term "spirocarbocyclic" or "spirocarbocycle" as used herein refers to a bicyclic hydrocarbon in which the ring pair has just one carbon-atom in common, which is designated the "spiro atom". Spirocarbocyclic compounds can be unsubstituted or substituted with one, two or three groups selected from loweralkyl, hydroxy, alkoxy, halo, haloalkyl and carboxy. Examples of spirocarbocycles include spiropentane, spirohexane, spiro[4.4]nonane, spiro[2.4]octane and the like.

The term "spiroheterocyclic" or "spiroheterocycle" as used herein refers to a bicyclic spirocyclic ring system containing carbon atoms and at least one heteroatom selected from oxygen, nitrogen and sulfur. Examples of spiroheterocycles include 1-oxa-4-azaspiro[5.4]decane, 1,4-diazaspiro[5.4]decane, 1-azaspiro[5.4]decane and the like. Spiroheterocyclics can be substituted in the same way as defined above for heterocyclics.

The term "tetrazolyl" as used herein refers to a radical of the formula



or a tautomer thereof.

The term "thioalkoxy" as used herein refers to $R_{70}S$- wherein R_{70} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

Representative compounds of the invention include:

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Cyclohexyloxycarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Oxa-4-azaspiro[4.5]decane-4-carboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Azaspiro[4.5]decane-4-carboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Methyl-N-phenylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Methyl-N-phenylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid methyl ester;

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)aminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(6-Fluoro-indol-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(6-Fluoro-1-indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(5-Fluoro-indol-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(5-Fluoro-1-indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Fluoro-1-indolylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Fluoro-1-indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(N-Cyclohexyl-N-methylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(1-Indolinylcarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Naphthylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Indolylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Benzofuran-2-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Isoquinolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Cyclohexylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Phenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(3-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(3-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(3-Quinolinylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-((2S)-(+)-2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2,6-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2,4-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-(4-isopropylbenzenesulfonyl)carboxamide;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-(methanesulfonyl)carboxamide;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(5-tetrazolyl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(5-tetrazolyl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid; and

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-thiazole-4-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

Preferred compounds are selected from the group consisting of:

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Cyclohexyloxycarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Azaspiro[4.5]decane-4-carboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Methyl-N-phenylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)aminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Fluoro-1-indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(N-Cyclohexyl-N-methylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(1-Indolinylcarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Naphthylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Cyclohexylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1S)-1-(N-(2R)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Phenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(3-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(3-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-((2S)-(+)-2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2,6-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;2-{(1R)-1-(N-(2S)-(2-(2,4-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid (4-isopropylbenzenesulfonyl)carboxamide;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid (methanesulfonyl)carboxamide;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(5-tetrazolyl)oxazole;

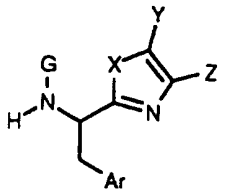
2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(5-tetrazolyl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid; and

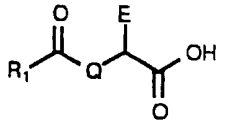
2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

One process for preparing the compounds of the invention comprises reacting a compound of the formula:



wherein Ar, G, X, Y and Z are as defined above with a compound of the formula:



or an activated derivative thereof,

wherein R_1, Q and E are as defined above.

Activated ester derivatives of carboxylic acids include acid halides such as acid chlorides, and activated esters including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

Additional processes for preparing the compounds of the invention are described below.

Methods for preparing the compounds of the invention are shown in Schemes I-VIII. The stereochemistry shown in the schemes is that of the preferred compounds of the invention. Compounds having other stereochemistry than that shown in the schemes can be obtained by starting with amino acids of opposite stereochemistry. In the following Schemes, X is -N(R_2)-, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl; and Y is hydrogen; loweralkyl; loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo; cycloalkyl; (cycloalkyl)alkyl; aryl; and arylalkyl.

The synthesis of one series of heterocycle containing peptides (where Q is -O-) is shown in Scheme I. The anion of carboxy protected N-(diphenylmethylene)glycine (P" is a carboxy protecting group, for example methyl, ethyl or benzyl) (1) is formed using a non-nucleophilic base (for example, lithium hexamethyldisilazide), and the anion is acylated with the appropriate acid chloride (for example, when Y is methyl, the acid chloride is acetyl chloride) to give upon acid workup the acylated glycine 2 as its ammonium salt. The acylated glycine is coupled with an appropriately protected activated amino acid residue (P* is an nitrogen protecting group, Ar is bicyclic aryl, aryl orbicyclic heteroaryl and A* is an amino acid activating group, for example, chloride, fluoride or mixed anhydride) to give 3. The heterocyclic ring is prepared using the appropriate reagents (for example, DBU, carbon tetrachloride and triphenylphosphine to prepare an oxazole; ammonium acetate to prepare an imidazole; and Lawesson's reagent to prepare a thiazole) to give compound 4. A similar route for the synthesis of heterocyclic dipeptide mimics has been described by Gordon, et al., Tetrahedron Lett. 34(12) 1901 (1993).

Hydroxy ester 6 (wherein R* is a carboxyl protecting group) is dissolved in an inert solvent (for example, THF) and converted to an activated compound 7 (where B* is an activating group, for example, an imidazolide formed by reaction of 6 with carbonyldiimidazole or an acid halide and the like). The activated compound 7 is optionally further activated (for example, by alkylation with methyl triflate) and when R_1 is a nucleophile (for example, an amine) it reacts directly with the activated carbonate to provide compound 8.

Alternatively R_1-CO_2H can be reacted directly with the protected hydroxy carboxylic acid 6 under standard esterification conditions. The carboxy protecting group is removed to afford R_1-C(O)-O-CH(E)-CO_2H (5). The heterocyclic intermediate 4 is nitrogen deprotected, coupled with the fully elaborated amino acid (R_1-C(O)-O-CH(E)-CO_2H) residue described above or an activated ester derivative thereof and then the carboxy protecting group is removed (for example, hydrolysis of an alkyl ester or hydrogenolysis of a benzyl ester) to give the final product 9.

Scheme II illustrates the preparation of compounds wherein Q is -CH_2-. Compound 21 (wherein R* is a carboxy protecting group) is prepared using the method of Plattner, et al., J. Med. Chem. 31 2277 (1988). The free carboxylic acid functionality of compound 21 is coupled or activated and reacted to give compound 22. For example, if R_1 is an amine, standard peptide coupling conditions, eg 1-hydroxybenzotriazole, N-methyl morpholine and EDCI, would give the desired product. Alternatively, one could make the acid chloride of the carboxylic acid and then react it with an organometallic compound to give the desired ketone. The carboxy protecting group is removed (for example, hydrolysis for an alkyl ester or hydrogenation for a benzyl ester) to give compound 23. Compound 23 is then coupled with compound 4, prepared in Scheme I, and then treated under conditions to remove the heterocyclic carboxy protecting group to give the final product 24.

Another approach is shown in Scheme III. Condensation of an amide 13 (X is O), thioamide 13 (X is S), or amidine 13 (X is NH), where Ar is bicyclic aryl or bicyclic heteroaryl and P* is an nitrogen protecting group, with α-halocarbonyl compound 13a (P" is a carboxy protecting group), followed by dehydration of the resultant aminol, provides compound 14. Deprotection of 14, coupling with an amino-terminal fragment, and carboxy deprotection, as described in Scheme I or II, gives the final product, 14a.

A preferred embodiment is shown in Scheme IV. The anion of N-(diphenylmethylene)glycine benzyl ester is formed using lithium hexamethyldisilazide and then is acylated with acetyl chloride to give the acyl glycine 16. The acylated glycine is coupled with an appropriately protected N-methyl-tryptophan to give 17. The heterocyclic ring is prepared using the appropriate reagents (for example, DBU, carbon tetrachloride and

triphenylphosphine to prepare an oxazole, ammonium acetate to prepare an imidazole and Lawesson's reagent to prepare a thiazole) to give compound 18. The heterocyclic intermediate is de-protected, coupled with compound 25 and the benzyl group hydrogenolyzed to give the final product 20.

The preparation of compound 25 is shown in Scheme V. L-Leucic acid is reacted with cesium carbonate and sodium carbonate in THF followed by benzyl bromide and DMF to give the α-hydroxy benzyl ester 26. Treatment of compound 26 in THF with carbonyldiimidazole affords imidazolide 27. The imidazolide is reacted with methyl trifluoromethanesulfonate in THF followed by the addition of cyclohexylamine to give carbamate 28. Catalytic hydrogenation removes the O-benzyl protecting group to give compound 25.

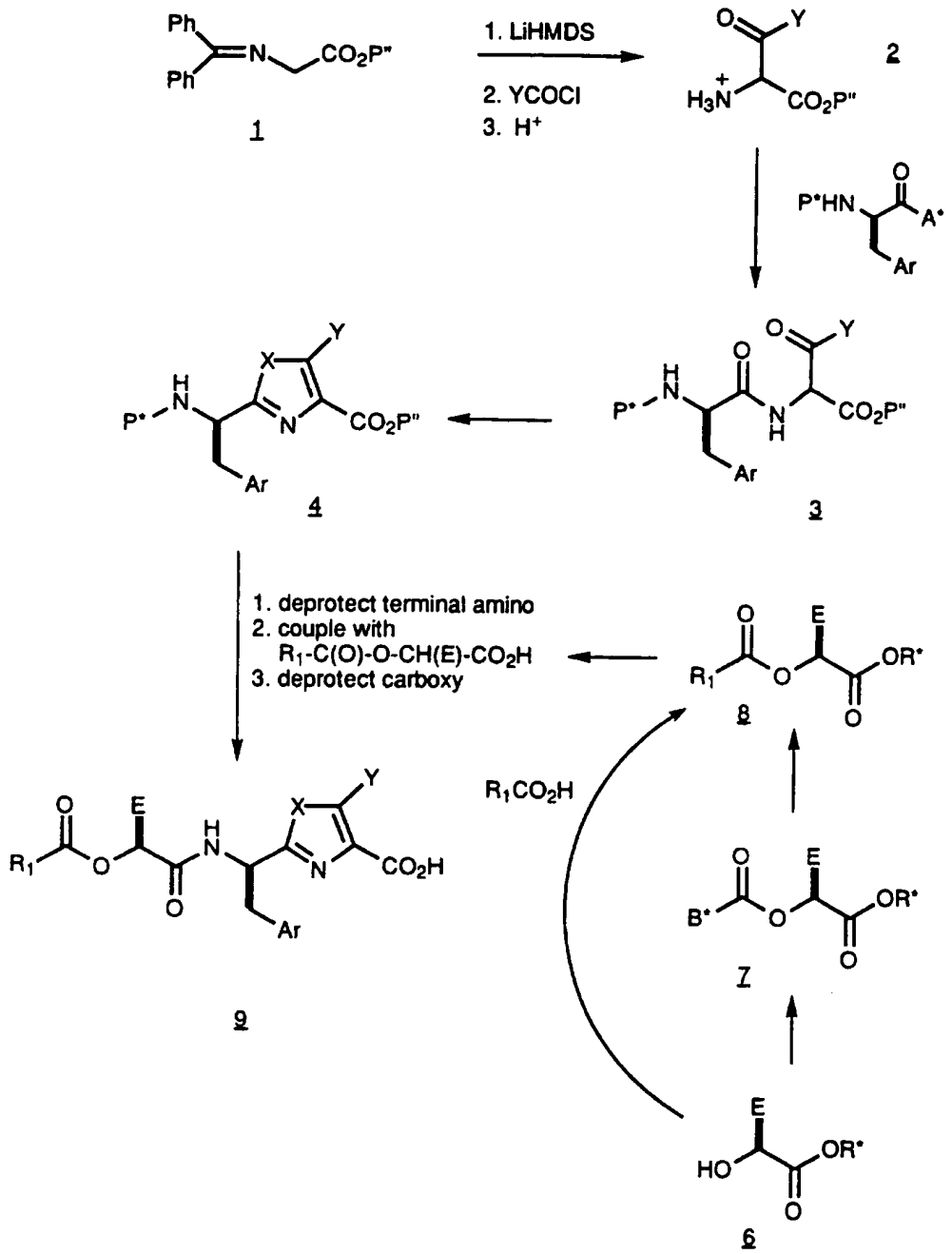
Another preferred embodiment is shown in Scheme VI. The α-hydroxy benzyl ester 26 prepared in Scheme V is reacted with 1-naphthoic acid in the presence of 1-hydroxybenzotriazole, EDCI and dimethylaminopyridine to give diester 31. The O-benzyl protecting group is removed using a palladium on carbon catalyst and 2 equivalents of cyclohexadiene in methanol to give the free carboxylic acid 32. Compound 32 is coupled with compound 18, prepared in Scheme IV, using N-methyl morpholine, EDCI and HOBt in THF/DMF, and then the O-benzyl protecting group is removed using the cyclohexadiene procedure described above to give the final product 33.

Scheme VII illustrates the preparation of compounds comprising various Z substituents. Compound 34, prepared for example by the procedures described in Scheme I, is dissolved in an inert solvent such as THF and reacted with carbonyldiimidazole followed by $R_{16}S(O)_2NH_2$ (wherein R_{16} is as defined previously herein) to give the corresponding sulfonamide 35. Alternatively, compound 36, prepared for example by the procedures described in Scheme II, is deprotected by catalytic hydrogenation of the benzyl ester and then reacted with isobutylchloroformate and ammonia in the presence of N-methylmorpholine to give the carboxamide compound. The carboxamide is dehydrated with phosphorus oxychloride to give the nitrile compound 37. The nitrile is deprotected (for example, using trifluoroacetic acid) and coupled under standard peptide coupling conditions (for example, 1-hydroxybenzotriazole, N-methylmorpholine, and EDCI) with carboxylic acid 38 to give amide 39. The nitrile compound is reacted with hydroxylamine hydrochloride in the presence

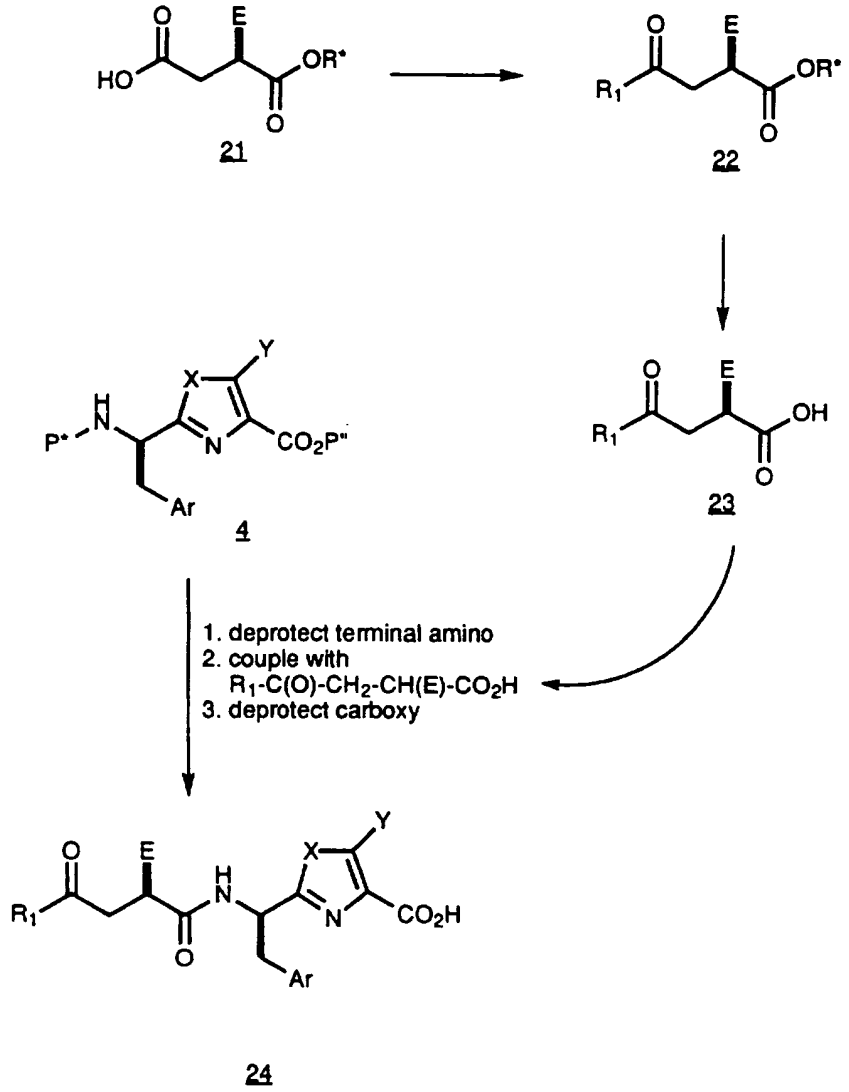
of ethanolic sodium ethoxide, followed by carbonyldiimidazole and a trace of DBU to give 4H-[1,2,4]oxadiazol-5-one 40. Alternatively, the nitrile 39 can be reacted with sodium azide in the presence of trimethyltin chloride to give tetrazole 41.

An alternate embodiment is shown in scheme VIII. The amine 18 prepared in Scheme IV is reacted with L-leucic acid in the presence of 1-hydroxybenzotriazole, EDCI and dimethylaminopyridine to afford the α-hydroxycarboxamide 42. This compound is then reacted with a carboxylic acid, for example, phenylacetic acid, in the presence of 1-hydroxybenzotriazole, EDCI and dimethylaminopyridine to afford the α-carboxycarboxamide 43. The O-benzyl protecting group is then removed as described in Scheme VI.

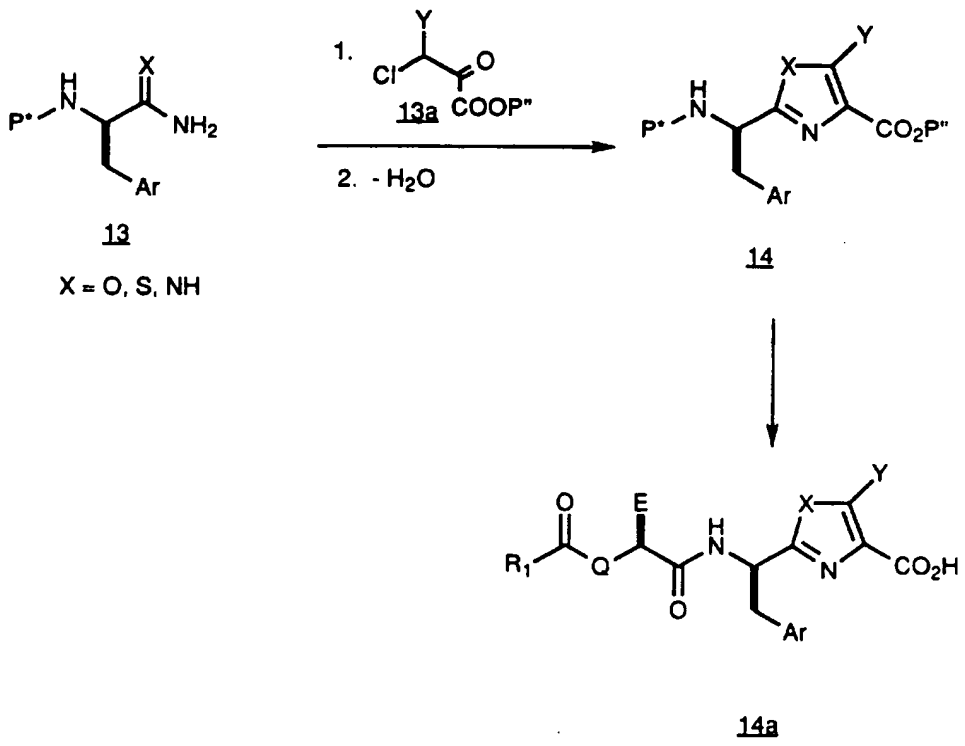
Scheme I


1. LiHMDS
2. YCOCl
3. H+
1
2
3
4
1. deprotect terminal amino
2. couple with
R1-C(O)-O-CH(E)-CO2H
3. deprotect carboxy
8
9
R1CO2H
7
6

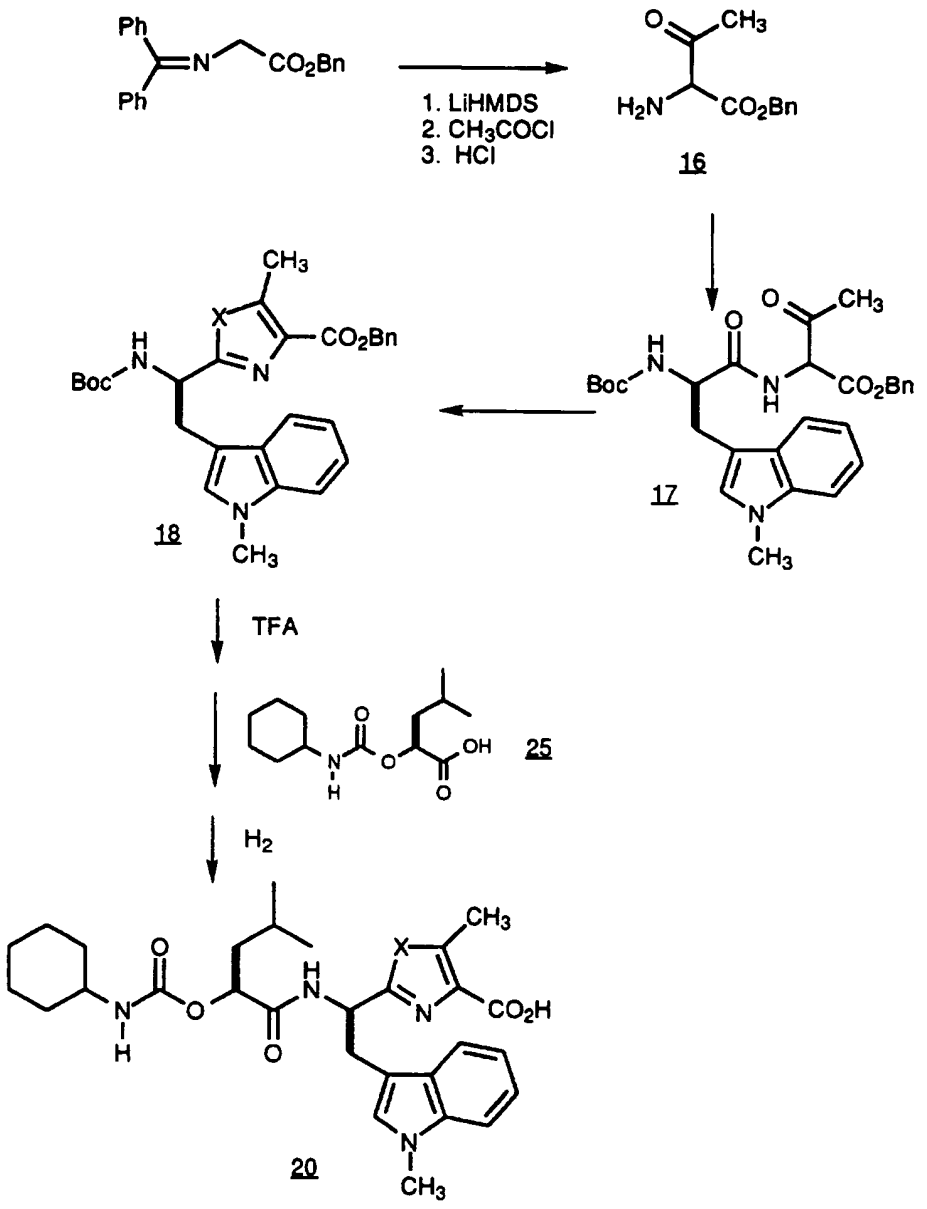
Scheme II


HO
O
E
OR*
21
R1
22
23
X
Y
N
H
P*
CO2P"
Ar
4
1. deprotect terminal amino
2. couple with
R1-C(O)-CH2-CH(E)-CO2H
3. deprotect carboxy
CO2H
24

Scheme III



Scheme IV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Ph
N
CO2Bn
1. LiHMDS
2. CH3COCl
3. HCl
O
CH3
H2N
CO2Bn
16
Boc
H
N
O
N
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CO2Bn
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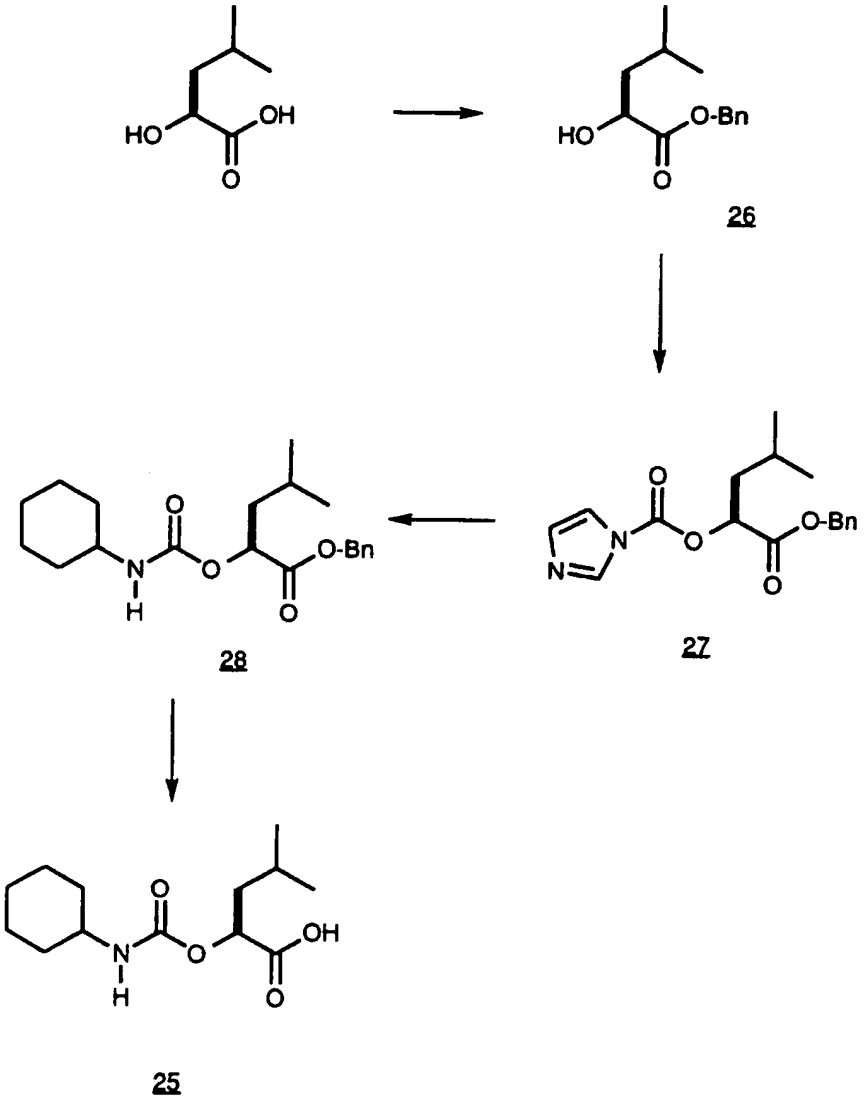
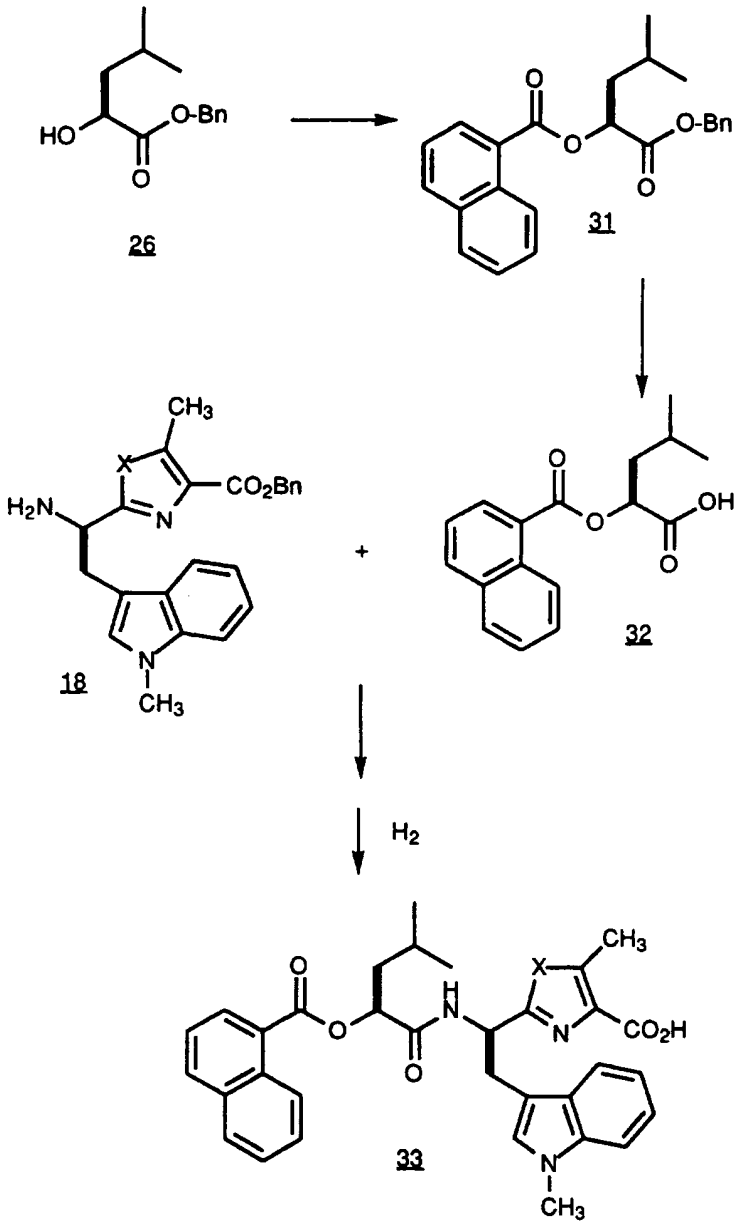
CH3
X
N
CO2Bn
18
TFA
OH
25
H2
20

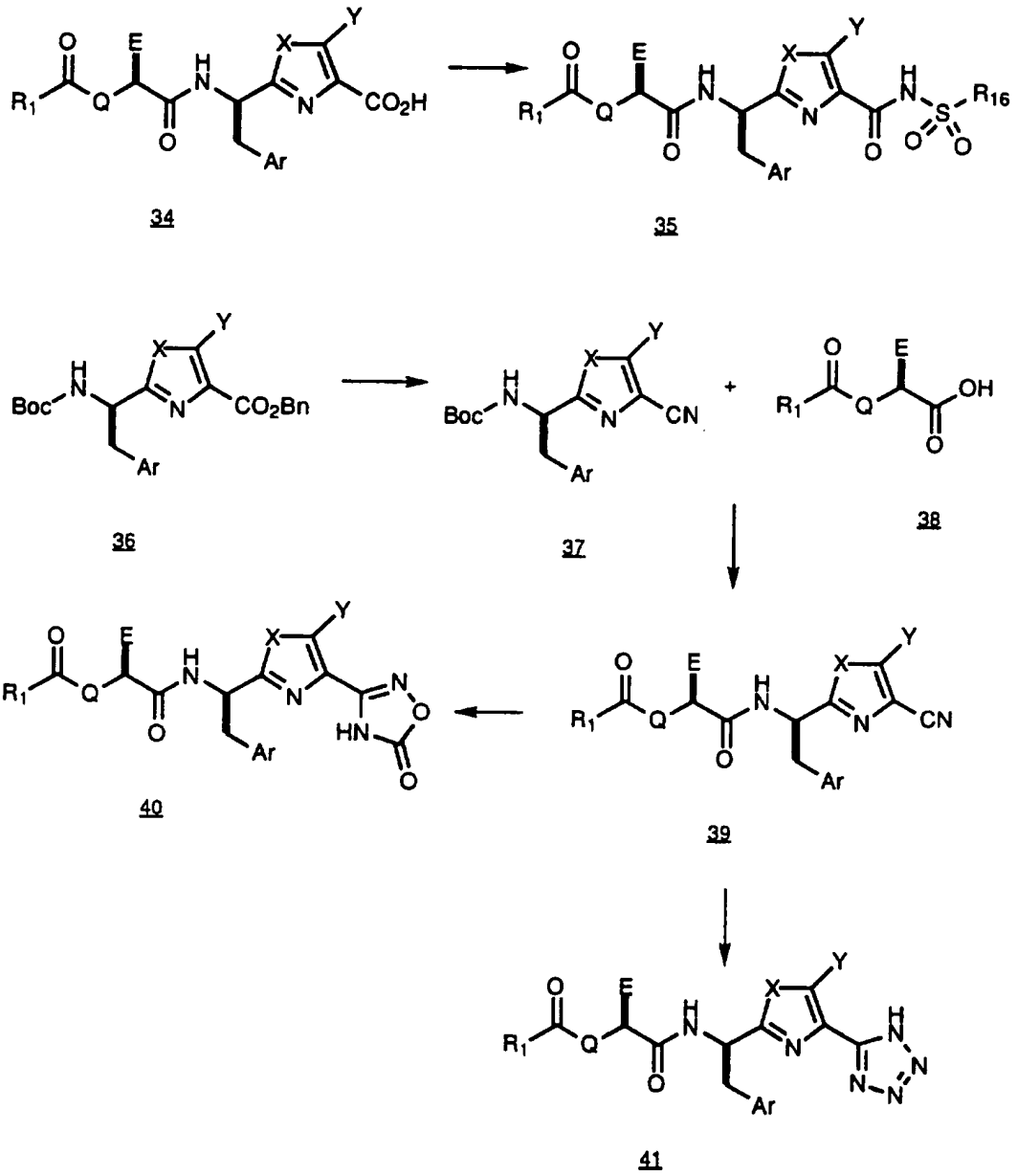
Scheme V



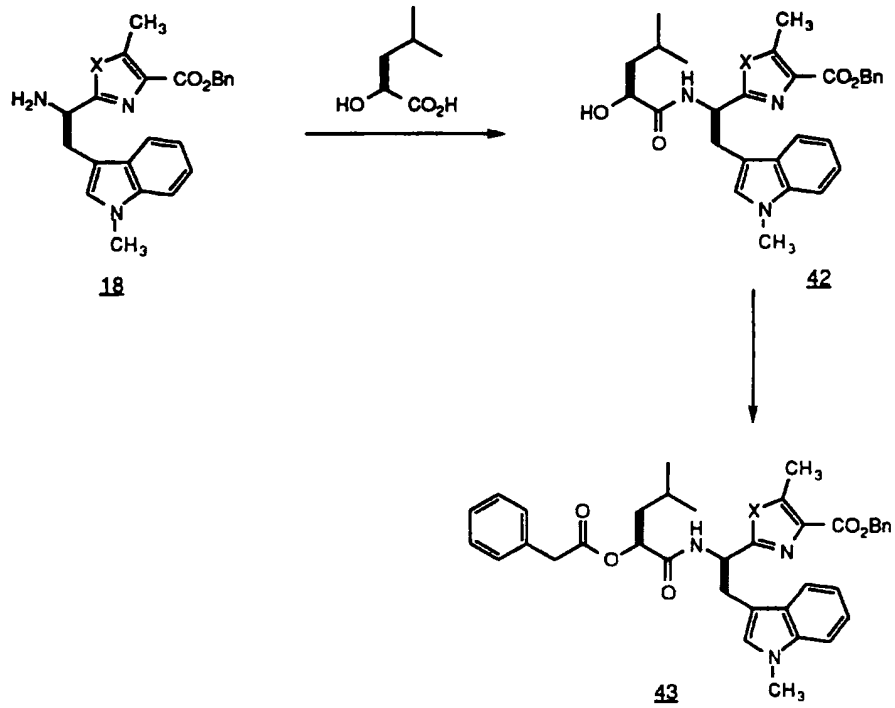
Scheme VI


HO
O-Bn
O
26
O
O
O-Bn
O
31
OH
32
CH3
X
CO2Bn
H2N
N
18
N
CH3
+
H2
CH3
X
CO2H
N
H
N
33
N
CH3

Scheme VII



Scheme VIII



The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept. The following abbreviations are used: Boc for tert-butyloxycarbonyl, Cbz for benzyloxycarbonyl, CDI for carbonyldiimidazole, Cha for cyclohexylalanine, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP for dimethylaminopyridine, EDCI for 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride, Et_3N for triethylamine, EtOAc for ethyl acetate, EtOH for ethanol, HOAc for acetic acid, HOBt for 1-hydroxybenzotriazole, LiHMDS for lithium hexamethyldisilazide, MeOH for methanol, NMM for N-

methylmorpholine, *p*-TsOH for *para*-toluenesulfonic acid, TFA for trifluoroacetic acid, Pd/C for palladium on carbon and THF for tetrahydrofuran.

Example 1

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

Example 1A

Boc-D-(1-Methyl)-Tryptophanyl-(2-acetylGlycine)-benzyl ester

N-(Diphenylmethylene)glycine benzyl ester (14.25 g) was dissolved in THF (175 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (43.25 mL, 1 N solution in THF) was added slowly over 15 minutes, and the resulting yellow slurry stirred at -78 °C for 45 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (3.4 mL) in THF (125 mL) at -78 °C. Complete transfer of the anion took about 30 minutes. After the addition was complete, the reaction was stirred at -78 °C for 30 minutes then allowed to warm to room temperature and stirred an additional three hours. The reaction was then quenched with 2 N HCl (50 mL). The THF was evaporated, and the resulting aqueous solution was washed with EtOAc (2 x 50 mL). The organic phases were discarded, and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (100 mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine benzyl ester hydrochloride as a yellow solid (10.48 g, 99% yield) which was used without further purification.

Boc-D-(1-methyl)-tryptophan (10.0 g) was dissolved in THF (75 mL) and the solution cooled to -20 °C. N-Methylmorpholine (3.45 mL) was added followed by the dropwise addition of isobutylchloroformate (4.0 mL). The 2-acetylglycine ester from above was dissolved in DMF (60 mL) and added to the mixed anhydride at -20 °C. N-Methylmorpholine (3.5 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (250 mL) was added and the mixture extracted with EtOAc (2 x 100 mL). The organic layer was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a yellow oil which

was purified by flash chromatography on silica gel eluting with 40% EtOAc-hexane. The product was isolated as a yellow oil (7.50 g, 47% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 2.18 (s, 1.5H), 2.24 (s, 1.5H), 3.17 (m, 1H), 3.20 (m, 1H), 3.74 (s, 3H), 4.50 (br s, 1H), 5.15 (m, 3H), 6.93 (d, 1H, J=7Hz), 7.11 (t, 1H, J=7Hz), 7.22 (t, 1H, J=7Hz), 7.33 (m, 6H), 7.59 (t, 1H, J=7Hz). MS (DCI/NH_3) m/e 508 $(M+H)^+$, 525 $(M+NH_4)^+$.

Example 1B

2-{(1R)-1-(Boc-Amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

The compound resulting from Example 1A (7.25 g) was dissolved in pyridine (25 mL), acetonitrile (25 mL), and carbon tetrachloride (3 mL). DBU (4.5 mL) and triphenylphosphine (4.20 g) were added and the mixture stirred at ambient temperature for 18 hours. The solvents were evaporated and the residue taken up in EtOAc (50 mL), washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting yellow oil was purified by flash chromatography on silica gel eluting with 30% EtOAc-hexane to give a pale yellow solid (4.35 g, 63%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H), 2.48 (s, 3H), 3.36 (m, 2H), 3.61 (s, 3H), 5.20 (m, 2H), 5.35 (s, 2H), 6.78 (br s, 1H), 7.03 (t, 1H, J=7Hz), 7.18 (t, 1H, J=7Hz), 7.24 (d, 1H, J=7Hz), 7.40 (m, 6H). MS (DCI/NH_3) m/e 490 $(M+H)^+$, 507 $(M+NH_4)^+$.

Example 1C

2-{(1R)-1-Amino-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

The compound resulting from Example 1B (120 mg) was dissolved in 6 mL of trifluoroacetic acid and allowed to stir at ambient temperature for 1 hour. The solvents were removed *in vacuo*; the residue was neutralized with sodium bicarbonate solution, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue obtained was used without further purification.

Example 1D

Benzyl (2S)-2-hydroxyisovalerate

A mixture of Cs_2CO_3 (10 g) and Na_2CO_3 (15 g) was suspended in 80 mL of THF, L-Leucic acid (10.0 g) was added, and the mixture was stirred for 20 minutes. Benzyl bromide (9.5 mL, 1.05 eq) was added, and the mixture was stirred for 15 hours at ambient temperature. DMF (20 mL) was added, and the mixture was heated at 40 °C for 3 hours. The mixture was taken up in 200 mL of water and extracted with 100 mL of EtOAc. The organic phase was washed twice with water, then once each with 1 N H_3PO_4 and brine, dried over Na_2SO_4, filtered through Celite®, and concentrated *in vacuo* to afford the title compound.

Example 1E

Benzyl (2S)-2-(Imidazol-1-ylcarboxy)isovalerate

The compound resulting from Example 1D (6.40 g) was combined in 75 mL of THF with 4.63 g (1.0 eq) of carbonyldiimidazole. The resultant solution was stirred at ambient temperature for 6 hours. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and then washed sequentially with 0.2 N H_3PO_4 and brine. The organic layer was dried over Na_2SO_4, filtered through Celite®, and evaporated *in vacuo* to give the title compound.

Example 1F

(2S)-2-(N-Cyclohexyl-N-methylaminocarboxy)isovaleric acid

The compound resulting from Example 1E (400 mg) was dissolved in 10 mL of THF and cooled to 0 °C. Methyl trifluoromethanesulfonate (0.14 mL, 1.0 eq) was added dropwise, and the solution was allowed to stir for 30 minutes. N-Methylcyclohexylamine (0.3 mL) was added, and the solution was allowed to warm to ambient temperature and stir for 12 hours. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with 1:1 sodium bicarbonate solution-water, 1 N H_3PO_4 and brine. The organic phase was dried over Na_2SO_4, filtered through Celite®, and concentrated *in vacuo* to give a yellowish oil. The crude product was purified by flash chromatography on silica gel eluting with 3:1 hexanes-ether, to give 302 mg of the benzyl ester as a colorless oil.

The benzyl ester was dissolved in 30 mL of ethanol, 80 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo* to provide 224 mg (65% overall yield) of the title compound.

Example 1G

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

To the compound resulting from Example 1C combined with 80 mg of the product resulting from Example 1F dissolved in 3 mL of THF and 3 mL of DMF were added 42 mg of HOBt, 8 drops of N-methyl morpholine, and 57 mg of EDCI. The resulting solution was stirred overnight at ambient temperature, and then the solvents were removed *in vacuo*. The residue was taken up in EtOAc, washed sequentially with 1:1 sodium bicarbonate solution-water, 1 N H_3PO_4 and brine, dried over Na_2SO_4, filtered through Celite®, and concentrated *in vacuo* to give a yellowish oil. Purification by flash chromatography eluting with 1:1 hexanes-EtOAc afforded the title compound.

Example 1H

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 1G was dissolved in 20 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo*. The residue was triturated with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (62 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 6H, J=7Hz), 1.0-1.8 (m, 13H), 2.55 (s, 3H), 2.75 (bd s, 3H), 3.32 (m, 1H), 3.43 (dd, 1H, J=7Hz,15Hz), 3.74 (s, 3H), 3.84 (m, 1H), 4.89 (dd, 1H, J=4Hz,10Hz), 5.20 (dd, 1H, J=7Hz,8Hz), 6.94 (s, 1H), 7.02 (ddd,

1H, J=1Hz,7Hz,8Hz), 7.13 (dt, 1H, J=1Hz,7Hz), 7.29 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 553 $(M+H)^+$, 570 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{40}N_4O_6 \cdot 0.9$ TFA: C, 58.29; H, 6.29; N, 8.55. Found: C, 58.54; H, 6.41; N, 8.67 .

Example 2

2-{(1R)-1-(N-(2S)-(2-(Cyclohexyloxycarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1, substituting cyclohexanol for N-methylcyclohexylamine in Example 1F. The crude final product was triturated with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (75 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J=6Hz), 0.85 (d, 3H, J=6Hz), 1.0-1.8 (m, 13H), 2.55 (s, 3H), 3.32 (m, 1H), 3.43 (dd, 1H, J=7Hz,15Hz), 3.74 (s, 3H), 4.47 (m, 1H), 4.83 (dd, 1H, J=5Hz,9Hz), 5.20 (dd, 1H, J=7Hz,9Hz), 6.96 (s, 1H), 7.02 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.14 (dt, 1H, J=1Hz,7Hz), 7.30 (d, 1H, J=8Hz), 7.48 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 540 $(M+H)^+$, 557 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{37}N_3O_7 \cdot 0.3$ TFA: C, 61.96; H, 6.55; N, 7.32. Found: C, 61.78; H, 6.66; N, 7.25.

Example 3

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1, substituting cyclohexylamine for N-methylcyclohexylamine in Example 1F. The crude material was purified by trituration with 2:1 hexanes-ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (103 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 3H, J=7Hz), 0.88 (d, 3H, J=7Hz), 1.0-1.9 (m, 13H), 2.55 (s, 3H), 3.3-3.5 (m, 2H), 3.73 (s, 3H), 4.92 (dd, 1H, J=5Hz,10Hz), 5.38 (dd, 1H, J=7Hz,8Hz), 6.93 (s, 1H), 7.00 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.13 (dt, 1H, J=1Hz,7Hz), 7.28 (d, 1H, J=8Hz), 7.44 (d, 1H, J=8Hz). MS (FAB/NBA)

m/e 539 $(M+H)^+$, 561 $(M+Na)^+$. Anal calcd for $C_{29}H_{38}N_4O_6 \cdot 0.3$ TFA: C, 62.06; H, 6.74; N, 9.78. Found: C, 61.66; H, 6.69; N, 9.89.

Example 4

2-{(1R)-1-(N-(2S)-(2-(1-Oxa-4-azaspiro[4.5]decane-4-carboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1, substituting 1-oxa-4-azaspiro[5.4]decane, prepared according to the procedure of Bergmann, et al., J. Amer. Chem. Soc. 75 358 (1953), for N-methylcyclohexylamine in Example 1F. The resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (85 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 6H, J=7Hz), 1.1-1.7 (m, 11H), 2.0-2.2 (m, 2H), 2.55 (s, 3H), 3.3-3.5 (m, 4H), 3.55 (m, 1H), 3.73 (s, 3H), 3.88 (t, 2H, J=7Hz), 5.40 (dd, 1H, J=7Hz,8Hz), 6.96 (s, 1H), 7.02 (dt, 1H, J=1Hz,8Hz), 7.14 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.29 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 581 $(M+H)^+$, 603 $(M+Na)^+$. Anal calcd for $C_{31}H_{40}N_4O_7 \cdot 0.6$ TFA: C, 59.59; H, 6.30; N, 8.63. Found: C, 59.55; H, 6.30; N, 8.69.

Example 5

2-{(1R)-1-(N-(2S)-(2-(1-Azaspiro[4.5]decane-1-carboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 5A

1-Azaspiro[4.5]decane

To a solution of 400 mg (2.67 mmol) of 1-azaspiro[4.5]decane-2-one (J. Am. Chem. Soc. 79 3186 (1957)) in 15 mL of THF was added 6 mL of 1 N BH_3 in THF. The solution was stirred at 0 °C for 3 hours and then heated at reflux for 2 hours. The solvents were removed *in vacuo*, and the residue was taken up in 15 mL of MeOH. Concentrated HCl (1 mL) was added, and the solution was stirred at ambient temperature overnight. The solvents were removed *in vacuo*; the residue was taken up in water and extracted with ether. The aqueous phase was basified with 2 N NaOH solution to pH 10, saturated with NaCl, and extracted with EtOAc. The combined organic extracts were concentrated *in*

vacuo to afford 100 mg of the title compound which was used without further purification.

Example 5B

2-{(1R)-1-(N-(2S)-(2-(1-Azaspiro[4.5]decane-1-carboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 substituting the compound resulting from Example 5A for N-methylcyclohexylamine in Example 1F. The resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (72 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 6H, J=7Hz), 1.1-1.9 (m, 15H), 2.0-2.2 (m, 2H), 2.54 (s, 3H), 3.3-3.5 (m, 4H), 3.73 (s, 3H), 4.87 (m, 1H), 5.38 (dd, 1H, J=6Hz,7Hz), 6.95 (s, 1H), 7.02 (dt, 1H, J=1Hz,7Hz), 7.14 (dt, 1H, J=1Hz,7Hz), 7.29 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 579 $(M+H)^+$, 596 $(M+NH4)^+$. Anal calcd for $C_{32}H_{42}N_4O_6 \cdot 0.8$ TFA: C, 60.24; H, 6.44; N, 8.36. Found: C, 60.47; H, 6.61; N, 8.40.

Example 6

2-{(1R)-1-(N-(2S)-(2-(N-Methyl-N-phenylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1, substituting N-methylaniline for N-methylcyclohexylamine in Example 1F. The crude final product was triturated with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (86 mg). ^{1}H NMR (CD_3OD, 300 MHz) of major rotamer δ 0.80 (broadened, 6H), 1.2-1.5 (m, 3H), 2.55 (s, 3H), 3.21 (bd s, 3H), 3.3-3.5 (m, 2H), 3.72 (s, 3H), 4.93 (dd, 1H, J=5Hz,10Hz), 5.40 (m, 1H), 6.96 (s, 1H), 7.03 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.12 (broad t, 1H, J=7Hz), 7.1-7.3 (m, 6H), 7.47 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 547 $(M+H)^+$, 564 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{34}N_4O_6 \cdot 0.7$ TFA: C, 60.21; H, 5.58; N, 8.94. Found: C, 59.98; H, 5.93; N, 8.91.

Example 7

2-{(1R)-1-(N-(2S)-(2-(N-Methyl-N-phenylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid methyl ester

The compound resulting from Example 6 (50 mg) was dissolved in 10 mL of ether and cooled to 0 °C, 3 mL of ethereal diazomethane (~0.3 M) was added, and the resultant yellowish solution was stirred for 1 hour. The solvents were removed *in vacuo*; the residue was purified by flash chromatography on silica gel eluting with 1:1 hexanes-EtOAc. The product was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (36 mg). ^{1}H NMR (CD_3OD, 300 MHz) of major rotamer δ 0.80 (broadened, 6H), 1.2-1.5 (m, 3H), 2.55 (s, 3H), 3.21 (bd s, 3H), 3.3-3.5 (m, 2H), 3.72 (s, 3H), 3.88 (s, 3H), 4.93 (dd, 1H, J=5Hz,10Hz), 5.40 (m, 1H), 6.96 (s, 1H), 7.03 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.12 (broad t, 1H, J=7Hz), 7.1-7.3 (m, 6H), 7.47 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 561 $(M+H)^+$, 578 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{36}N_4O_6 \cdot 0.2$ TFA: C, 64.64; H, 6.25; N, 9.60. Found: C, 64.34; H, 6.37; N, 9.56.

Example 8

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)aminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 8A

Benzyl (2S)-2-(N-(2-fluorophenyl)aminocarboxy)-isovalerate

Benzyl (2S)-2-hydroxyisovalerate (0.56 g, 2.5 mmol), prepared as described in Example 1D, 2-fluorophenylisocyanate (0.34 g, 1.0 eq), and 0.2 mL of N-methyl morpholine were combined in 5 mL of THF and stirred at ambient temperature for 16 hours. The solvents were removed *in vacuo*; the residue was taken up in EtOAc, then washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine. The crude product was dissolved in 20 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature

for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The residue was taken up in ether and extracted with 1 N NaOH. The basic extracts were acidified with 1 N H_3PO_4 and extracted with EtOAc. The combined organic extracts were concentrated *in vacuo* to give 600 mg (89% yield) of the title compound.

Example 8B

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)aminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

To the product resulting from Example 1C combined with 80 mg of the product resulting from Example 8A in 3 mL of THF and 3 mL of DMF were added sequentially 42 mg of HOBt, 8 drops of N-methyl morpholine, and 57 mg of EDCI. The resultant solution was stirred overnight at ambient temperature, and the solvents were removed *in vacuo*. The residue was taken up in EtOAc and washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine, dried over Na_2SO_4, filtered through Celite®, and concentrated *in vacuo* to give crude title compound as a yellowish oil, which was purified by flash chromatography eluting with 1:1 hexanes-EtOAc.

Example 8C

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)aminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 8B was dissolved in 20 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (65 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J=6Hz), 0.91 (d, 3H, J=6Hz), 1.46 (m, 1H), 1.66 (m, 2H), 2.56 (s, 3H), 3.34 (dd, 1H, J=9Hz,15Hz), 3.45 (dd, 1H, J=6Hz,15Hz), 3.60 (s, 3H), 5.06 (dd, 1H, J=5Hz,9Hz), 5.41 (dd, 1H, J=6Hz,9Hz), 6.92 (s, 1H), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.05-7.2 (m, 4H), 7.24 (dt, 1H, J=1Hz,8Hz), 7.44 (d, 1H, J=8Hz), 7.83 (m, 1H). MS (FAB/NBA) m/e

551 $(M+H)^+$, 573 $(M+Na)^+$. Anal calcd for $C_{29}H_{31}N_4O_6F \cdot 0.4$ TFA: C, 60.04; H, 5.31; N, 9.40. Found: C, 59.95; H, 5.31; N, 9.00.

Example 9

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

Example 9A

2-Fluoro-N-methylaniline

The title compound was prepared according to the procedures described in Org Syn IV 420, except substituting o-fluoroaniline for p-chloroaniline and trimethyl orthoformate for triethyl orthoformate. The product was purified by distillation (b.p. 68-70 °C at 3 mm Hg).

Example 9B

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1, substituting the compound resulting from Example 9A for N-methylcyclohexylamine in Example 1F. The crude final product was triturated with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder. ^1H NMR ($CDCl_3$-CD_3OD, 300 MHz) δ 0.60-0.95 (m, 6H), 1.2-1.4 (m, 3H), 2.58 (s, 3H), 3.20 (s, 3H), 3.2-3.4 (m, 2H), 3.75 (s, 3H), 4.90 (m, 1H), 5.42 (m, 1H), 6.86 (s, 1H), 7.05-7.25 (m, 6H), 7.50 (d, 1H, J=7Hz). MS (FAB) m/e 565 $(M+H)^+$, 587 $(M+Na)^+$, 609 $(M+2Na-H)^+$. Anal calcd for $C_{30}H_{33}N_4O_6F \cdot 0.5$ TFA: C, 59.90; H, 5.43; N, 9.01. Found: C, 60.26; H, 5.82; N, 8.74.

Example 10

2-{(1R)-1-(N-(2S)-(2-(1-Indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1, substituting indoline for N-methylcyclohexylamine in Example 1F. The crude final product was triturated with hexanes/ether; the resultant material

was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (78 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.88 (d, 6H, J=7Hz), 1.4-1.8 (m, 3H), 2.56 (s, 3H), 3.07 (m, 2H), 3.3-3.5 (m, 2H), 3.60 (s, 3H), 3.79 (t, 2H, J=9Hz), 5.06 (m, 1H), 5.23 (dd, 1H, J=7Hz,8Hz), 6.90 (s, 1H), 6.9-7.2 (m, 6H), 7.43 (d, 1H, J=8Hz), 7.71 (m, 1H). MS (DCI/NH_3) m/e 553 $(M+H)^+$, 570 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{34}N_4O_6 \cdot 0.7$ TFA: C, 60.96; H, 5.48; N, 8.78. Found: C, 60.87; H, 5.77; N, 8.89.

Example 11

2-((1R)-1-(N-(2S)-(2-(6-Fluoro-indol-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

Example 11A

Benzyl (2S)-2-(6-fluoro-indol-1-ylcarboxy)isovalerate

To the compound resulting from Example 1E (300 mg) dissolved in 6 mL of nitromethane and cooled to 0 °C was added dropwise methyl trifluoromethanesulfonate (0.11 mL, 1.0 eq). The solution (solution A) was stirred for 30 minutes at 0 °C, then cooled to -50 °C. Simultaneously a suspension of sodium hydride (30 mg of 80% oil dispersion; 1.0 mmol) in 2 mL of THF was cooled to 0 °C, and 6-fluoroindole (135 mg, 1.0 eq) was added in five portions. The resultant solution (solution B) was warmed to ambient temperature over 30 minutes, then cooled back to 0 °C and transferred dropwise into solution A. The reaction mixture was stirred for 1 hour at -50 °C. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc. The solution was washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 10% EtOAc-hexanes, to give 163 mg (45% yield) of the title compound along with 73 mg (24%) of recovered 6-fluoroindole.

Example 11B

(2S)-2-(6-Fluoro-indol-1-ylcarboxy)isovaleric acid

Cyclohexadiene (0.1 mL) was added to a suspension of 60 mg of 10% Pd/C in 2 mL of MeOH. The mixture was stirred for 10 minutes, and then a solution of the compound resulting from Example 11A (108 mg) in 2 mL of 1:1 MeOH-EtOAc was added. The resultant suspension was stirred for 2 hours at ambient temperature. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo* to give the title compound, which was used without further purification.

Example 11C

2-{(1R)-1-(N-(2S)-(2-(6-Fluoro-indol-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

To the product resulting from Example 1C combined with 80 mg of the product resulting from Example 11B in 3 mL of THF and 3 mL of DMF were added sequentially 42 mg of HOBt, 8 drops of N-methyl morpholine, and 57 mg of EDCI. The resultant solution was stirred overnight at ambient temperature, and the solvents were removed *in vacuo*. The residue was taken up in EtOAc and washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine. The organic phase was dried over Na_2SO_4, filtered through Celite®, and concentrated to give a yellowish oil, which was purified by flash chromatography eluting with 3:1 going to 2:1 hexanes-EtOAc.

Example 11D

2-{(1R)-1-(N-(2S)-(2-(6-Fluoro-indol-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Cyclohexadiene (0.1 mL) was added to a suspension of 50 mg of 10% Pd/C in 2 mL of MeOH. The mixture was stirred for 5 minutes, and then a solution of the product resulting from Example 11C in 3 mL of 1:1 MeOH-EtOAc was added. The resultant suspension was stirred for 2 hours at ambient temperature. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The residue was triturated with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (22 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.88 (d, 6H, J=6Hz), 1.4-1.8 (m, 3H),

2.56 (s, 3H), 3.3-3.5 (m, 2H), 3.62 (s, 3H), 5.23 (dd, 1H, J=4Hz,9Hz), 5.45 (dd, 1H, J=6Hz,8Hz), 6.66 (d, 1H, J=4Hz), 6.92 (s, 1H), 6.94 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.0-7.1 (m, 2H), 7.24 (d, 1H, J=8Hz), 7.46 (d, 1H, J=8Hz), 7.55 (dd, 1H, J=6Hz,9Hz), 7.65 (d, 1H, J=4Hz), 7.82 (dd, 1H, J=2Hz,10Hz). MS (FAB/NBA) m/e 575 $(M+H)^+$, 597 $(M+Na)^+$. HRMS calcd for $C_{31}H_{32}N_4O_6F$: 575.2306. Found: 575.2302.

Example 12

2-{(1R)-1-(N-(2S)-(2-(6-Fluoro-indolin-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 12A

(2S)-2-(6-Fluoro-indol-1-ylcarboxy)-isovaleric acid benzyl ester

A sample of the compound resulting from Example 1E (300 mg) was dissolved in 6 mL of nitromethane and cooled to 0 °C; methyl trifluoromethanesulfonate (0.11 mL, 1.0 eq) was added dropwise. The solution (solution A) was stirred for 30 minutes at 0 °C, then cooled to -50 °C. Simultaneously a suspension of sodium hydride (30 mg of 80% oil dispersion: 1.0 mmol) in 2 mL of THF was cooled to 0 °C; 6-fluoroindole (135 mg, 1.0 eq) was added in five portions. The resultant solution (solution B) was warmed to ambient temperature over 30 minutes, then cooled back to 0 °C and transferred dropwise into solution A. The reaction mixture was stirred for 1 hour at -50 °C. The solvents were removed *in vacuo*; the residue was taken up in EtOAc, then washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine, dried and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 10% EtOAc-hexanes to give 163 mg (45% yield) of the title compound along with 73 mg (24%) of recovered 6-fluoroindole.

Example 12B

(2S)-2-(6-Fluoro-indolin-1-ylcarboxy)-isovaleric acid

The product resulting from Example 12A (108 mg) was dissolved in 10 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo* to give the title compound, which was used without further purification.

Example 12C

2-{(1R)-1-(N-(2S)-(2-(6-Fluoro-indolin-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

To the product resulting from Example 1C combined with 80 mg of the product of Example 12B in 3 mL of THF and 3 mL of DMF were added sequentially 42 mg of HOBt, 8 drops of N-methyl morpholine, and 57 mg of EDCI. The resultant solution was stirred overnight at ambient temperature, and the solvents were removed *in vacuo*. The residue was taken up in EtOAc and washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine. The organic phase was dried over Na_2SO_4, filtered through Celite®, and concentrated to give a yellowish oil, which was purified by flash chromatography eluting with 3:1 going to 2:1 hexanes-EtOAc.

Example 12D

2-{(1R)-1-(N-(2S)-(2-(6-Fluoro-indolin-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 12C was dissolved in 20 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (74 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.8 (d, 6H, J=6Hz), 1.4 (m, 1H), 1.65 (m, 2H), 2.57 (s, 3H), 3.03 (m, 2H), 3.3-3.5 (m, 2H), 3.65 (s, 3H), 3.92 (t, 2H, J=9Hz), 4.93 (dd, 1H, J=5Hz,10Hz), 5.06 (dd, 1H, J=4Hz,9Hz), 5.43 (dd, 1H,

J=6Hz,8Hz), 6.68 (dt, 1H, J=2Hz,9Hz), 6.93 (s, 1H), 6.95 (t, 1H, J=8Hz), 7.06 (m, 1H), 7.13 (dd, 1H, J=6Hz,8Hz), 7.22 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 577 $(M+H)^+$, 599 $(M+Na)^+$. Anal calcd for $C_{31}H_{33}N_4O_6F \cdot 0.5$ TFA: C, 60.66; H, 5.33; N, 8.84. Found: C, 60.42; H, 5.56; N, 8.76.

Example 13

2-{(1R)-1-(N-(2S)-(2-(5-Fluoro-indol-1-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 11, substituting 5-fluoroindole for 6-fluoroindole in Example 11A. The resultant material was dissolved in water/acetonitrile and lyophilized to give the title compound as a white powder. The ^1H NMR (CD_3OD, 300 MHz) was consistent with the expected structure. HRMS (FAB) Calculated for $C_{31}H_{31}N_4O_6FNa$: 597.2125. Found: 597.2116.

Example 14

2-{(1R)-1-(N-(2S)-(2-(5-Fluoro-1-indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 12, substituting 5-fluoroindole for 6-fluoroindole in Example 12A. The resultant material was dissolved in water/acetonitrile and lyophilized to give the title compound as a white powder. ^1H NMR (300 MHz, CD_3OD) δ 7.61 (1H, m), 7.49 (1H, d, J=8Hz), 7.21 (1H, d, J=7Hz), 6.96 (5H, m), 5.39 (1H, bt, J=7Hz), 5.25 (1H, m), 3.56 (3H, s), 3.39 (1H, dd, J=8Hz,6Hz), 2.98 (1H, m), 2.54 (3H, s), 1.61 (2H, m), 1.41 (1H, m), 0.91 (3H, d, J=7Hz), 0.89 (1H, d, J=7Hz). MS (DCI/NH_3) m/e 577 $(M+H)^+$, 594 $(M+H+NH_3)^+$.

Example 15

2-{(1R)-1-(N-(2S)-(2-(4-Fluoro-1-indolylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 11, substituting 4-fluoroindole for 6-fluoroindole in Example 11A. The resultant material was dissolved in water/acetonitrile and lyophilized to give the title compound as a white powder. ^1H NMR (300 MHz, CD_3OD) δ (1H,

d, J=9Hz), 7.29 (1H, td, J=9Hz,7Hz), 7.21 (1H, d, J=9Hz), 7.16 (1H, dt, J=3Hz,9Hz), 6.97 (3H, m), 6.73 (1H, d, J=7Hz), 5.43 (1H, dd, J=7Hz,5Hz), 5.26 (1H, dd, J=9Hz,7Hz), 3.61 (s, 3H), 3.34 (3H, m), 2.55 (3H, s), 1.76 (3H, m), 1.49 (1H, m), 0.92 (6H, d, J=7Hz). MS (FAB) m/e 597 $(M+Na)^+$. Anal calc for $C_{31}H_{31}FN_4O_6$. 1.5 H_2O: C, 61.89; H, 5.70; N, 9.31. Found: C, 61.64; H, 5.32; N, 9.00.

Example 16

2-[(1R)-1-(N-(2S)-(2-(4-Fluoro-1-indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 12, substituting 4-fluoroindole for 6-fluoroindole in Example 12A. The resultant material was dissolved in water/acetonitrile and lyophilized to give the title compound as a white powder. ^1H NMR (300 MHz, CD_3OD) δ 7.34 (1H, d, J=9Hz), 7.18 (1H, m), 7.04 (1H, m), 6.94 (1H, m), 6.92 (1H, m), 6.73 (1H, t, J=8Hz), 5.42 (1H, dd, J=7Hz,5Hz), 5.09 (1H, dd, J=9Hz,7Hz), 3.93 (1H, bt, J=8Hz), 3.61 (3H, s), 3.39 (2H, s), 3.02 (1H, m), 2.57 (3H, s), 1.66 (2H, m), 1.41 (1H, m), 0.89 (6H, d, J=7Hz). MS (DCI/NH_3) m/e 594 $(M+H+NH_3)^+$. Anal calc for $C_{31}H_{33F}N_4O_6$. 2H_2O: C, 60.78; H, 6.09; N, 9.14. Found: C, 60.39; H, 5.78; N, 8.71.

Example 17

2-[(1R)-1-(N-(2R)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

Example 17A

(2R)-2-(N-Cyclohexylaminocarbonylmethyl)-isovaleric acid

To a solution of (3R)-3-benzyloxycarbonyl-5-methylhexanoic acid (464 mg), prepared by the method of Plattner, et al., J. Med. Chem. 31 2277-88 (1988) but substituting isovaleryl chloride for 3-phenylpropionyl chloride, and 0.23 mL (1 eq) of cyclohexylamine in 20 mL of 3:1 THF-DMF were added sequentially 270 mg (1 eq) of HOBt, 1.2 mL of N-methyl morpholine, and 384 mg (1 eq) of EDCI. The resultant solution was stirred at ambient temperature for 15 hours, the solvents were removed *in vacuo*, and the residue was taken

up in EtOAc. The resulting solution was washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine, dried over Na_2SO_4, filtered through Celite®, and concentrated *in vacuo*.

To the crude ester dissolved in 50 mL of ethanol was added 100 mg of 10% palladium on carbon. The mixture was purged with nitrogen, the nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo* to provide the title compound.

Example 17B

2-{(1R)-1-(N-(2R)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

To the product resulting from Example 1C combined with 80 mg of the product resulting from Example 17A in 3 mL of THF and 3 mL of DMF were added sequentially 42 mg of HOBt, 8 drops of N-methyl morpholine, and 57 mg of EDCI. The resultant solution was stirred overnight at ambient temperature, and the solvents were removed *in vacuo*. The residue was taken up in EtOAc and washed sequentially with 1:1 sodium bicarbonate solution/water, 1 N H_3PO_4 and brine. The organic phase was dried over Na_2SO_4, filtered through Celite®, and concentrated to give crude title compound as a yellowish oil, which was purified by flash chromatography eluting with 3:1 going to 2:1 hexanes-EtOAc.

Example 17C

2-{(1R)-1-(N-(2R)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 17B was dissolved in 20 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The crude material was purified by trituration with hexanes/ether; the resultant material was dissolved in 0.1% aqueous

TFA/acetonitrile and lyophilized to give the title compound as a white powder (76 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.70 (d, 6H, J=7Hz), 1.0-1.4 (m, 8H), 1.5-1.8 (m, 5H), 2.12 (dd, 1H, J=7Hz,14Hz), 2.31 (dd, 1H, J=8Hz,14Hz), 2.54 (s, 3H), 2.71 (m, 1H), 3.2-3.4 (m, 2H), 3.50 (m, 1H), 3.73 (s, 3H), 5.45 (dd, 1H, J=7Hz,9Hz), 6.99 (s, 1H), 7.02 (dt, 1H, J=1Hz,7Hz), 7.13 (dt, 1H, J=1Hz,7Hz), 7.29 (d, 1H, J=8Hz), 7.52 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 537 $(M+H)^+$, 554 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{40}N_4O_5 \cdot 1.0$ TFA $\cdot 1.5$ H_2O: C, 56.71; H, 6.54; N, 8.27. Found: C, 56.74; H, 6.08; N, 8.73.

Example 18

2-[(1R)-1-(N-(2R)-(2-(N-Cyclohexyl-N-methylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 17, substituting N-methylcyclohexylamine for cyclohexylamine in Example 17A. The crude material was purified by trituration with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.70 (m, 6H), 1.1-1.7 (m, 13H), 2.15 (m, 2H), 2.55 (s, 3H), 2.80 (s, 3H), 3.2-3.4 (m, 2H), 3.65 (m, 1H), 3.75 (s, 3H), 4.20 (m, 1H), 5.42 (m, 1H), 7.00 (s, 1H), 7.01 (dd, 1H, J= 1Hz,7Hz), 7.15 (dd, 1H, J= 1Hz,7Hz), 7.30 (d, 1H, J=7Hz), 7.52 (dd, 1H, J= 1Hz,7Hz). MS (DCI/NH_3) m/e 551 $(M+H)^+$, 568 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{42}N_4O_5 \cdot 0.8$ TFA: C, 61.00; H, 6.72; N, 8.73. Found: C, 61.13; H, 7.03; N, 8.34.

Example 19

2-[(1R)-1-(N-(2R)-(2-(1-Indolinylcarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 17, substituting indoline for cyclohexylamine in Example 17A. The crude material was purified by trituration with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.68 (d, 6H, J=7Hz), 1.25 (m, 2H), 1.40 (m, 1H), 2.45 (s, 3H), 2.55 (m, 1H), 3.05 (m, 2H), 3.25 (m, 2H), 3.60 (m, 1H), 3.75 (s, 3H), 3.85 (m, 2H), 4.30 (m, 1H), 5.42

(dd, 1H, J=6Hz,7Hz), 7.00 (m, 3H), 7.15 (m, 3H), 7.25 (d, 1H, J=7Hz), 7.58 (d, 1H, J= 7Hz). MS (DCI/NH_3) m/e 557 $(M+H)^+$, 574 $(M+NH_4)^+$. Anal calcd for $C_{32}H_{36}N_4O_5 \cdot 2.1\ H_2O$: C, 64.65; H, 6.82; N, 9.42. Found: C, 64.69; H, 6.76; N, 9.14.

Example 20

2-{(1R)-1-(N-(2S)-(2-(1-Naphthylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

Example 20A

Benzyl (2S)-2-(1-naphthylcarboxy)-isovalerate

To a stirred solution of benzyl 2-hydroxyisovalerate (100 mg, 0.45 mmol) in THF (3 mL) and DMF (5 mL) were added successively 1-naphthalenecarboxylic acid (78 mg, 0.49 mmol, 1.0 eq), HOBt (95 mg, 0.49 mmol, 1.1eq), EDCI (95mg, 0.45 mmol, 1.1 eq), and DMAP (55 mg, 0.45 mmol, 1eq). The resultant solution was stirred at room temperature overnight, then poured into ethyl acetate, and washed successively with saturated aqueous sodium bicarbonate solution, 1 N phosphoric acid and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was flash chromatographed on silica gel eluting with 5% EtOAc-hexanes to yield the title compound (118 mg, 70%) as a colorless oil.

Example 20B

(2S)-2-(1-Naphthylcarboxy)-isovaleric acid

To a suspension of 10% palladium on carbon (50 mg) in methanol (2 mL) was added successively a solution of the compound resulting from Example 20A (118 mg, 0.31 mmol) and cyclohexa-1,3-diene (0.06 mL, 0.62 mmol, 2 eq). The mixture was stirred at room temperature for 16 hours, after which time the catalyst was removed by filtration through Celite®. The solvent was removed *in vacuo* to afford the title compound (81 mg, 90%).

Example 20C

2-{(1R)-1-(N-(2S)-(2-(1-Naphthylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

To a solution of the compound prepared in Example 1C (120 mg, 0.283 mmol, 1 eq) in THF (3 mL) and DMF (6 mL) was added successively the compound resulting from Example 20B (81 mg, 0.283 mmol, 1 eq), N-methyl morpholine (0.034 mL, 0.31 mmol, 1.1 eq), HOBt (42 mg, 0.31 mmol, 1.1 eq), and EDCI (60 mg, 0.28 mmol, 1 eq). The reaction was stirred at room temperature overnight and was then poured into EtOAc and washed successively with saturated aqueous sodium bicarbonate solution, 1 N phosphoric acid, and brine. The solution was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was flash chromatographed on silica gel eluting with 30% EtOAc-hexanes to yield the title compound (157 mg, 84%) as a colorless oil.

Example 20D

2-{(1R)-1-(N-(2S)-(2-(1-Naphthylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

To a suspension of 10% palladium on charcoal (80 mg) in methanol (4 mL) was added a solution of the compound resulting from Example 20C (151 mg, 0.239 mmol) in ethyl acetate (8 mL) followed by cyclohexadiene (0.046 mL, 0.478 mmol, 2 eq). The mixture was stirred overnight, after which time the catalyst was removed by filtration through Celite®. The solvent was removed *in vacuo*, and the residue was dissolved in acetonitrile, diluted with water, frozen, and lyophilized to yield the title compound as a white solid (116 mg, 86%). ^1H NMR (300 MHz, CD_3OD) δ 8.78 (1H, m), 8.25 (1H, dd, J=8Hz,3Hz), 8.18, (1H, d, J=8Hz), 7.92 (1H, dd, J=8Hz,3Hz), 7.55 (2H, dt, J=8Hz,3Hz), 7.45 (2H, m), 7.20, (1H, m), 7.20 (1H, d, J=8Hz), 7.17 (td, J=3Hz,8Hz), 6.94 (td, J=3Hz,8Hz), 6.91 (1H, s), 5.44 (dd, J=7Hz,5Hz), 5.31 (dd, J=9Hz,7Hz), 3.54 (3H, s), 3.34 (3H, m), 2.55 (3H, s), 1.76 (3H, m), 1.49 (1H, m), 0.92 (6H, d, J=7Hz). MS (DCI/NH_3) m/e 568 $(M+H)^+$, 585 $(M+H+NH_3)^+$. Anal calc for $C_{33}H_{33}N_3O_6 \cdot 2H_2O$: C, 64.70; H, 6.25; N, 6.32. Found: C, 65.08; H, 5.84; N, 6.32.

Example 21

2-((1R)-1-(N-(2S)-(2-(2-Indolylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared using the procedures described in Example 20, substituting indole-2-carboxylic acid for 1-naphthoic acid in Example 20A. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.67 (1H, d, J=9Hz), 7.44 (1H, d, J=9Hz), 7.38 (1H, d, J=8Hz), 7.29 (1H, dt, J=8Hz,2Hz), 7.23 (1H, s), 7.17 (1H, d, J=8Hz), 7.11 (1H, dt, J=8Hz,3Hz), 7.03 (1H, J=8Hz), 6.89 (1H, t, J=8Hz), 6.88 (1H, s), 5.42 (1H, dd, J=7Hz,5Hz), 5.29 ((1H, dd, J=9Hz,7Hz), 3.44 (3H, s), 3.39 (2H, s), 2.57 (3H, s), 1.66 (2H, m), 1.41 (1H, m), 0.89 (6H, d, J=7Hz). MS (DCI/NH_3) m/e 557 $(M+H)^+$, 574 $(M+H+NH_3)^+$. Anal calc for $C_{31}H_{32}N_4O_6$. 0.5 TFA: C, 62.64; H, 5.34; N, 9.13. Found: C, 62.81; H, 5.43; N, 8.77.

Example 22

2-((1R)-1-(N-(2S)-(2-(Benzofuran-2-ylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared using the procedures described in Example 20, substituting benzofuran-2-carboxylic acid for 1-naphthoic acid in Example 20A. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.75 (1H, d, J=8Hz), 7.64 (1H, d, J=2Hz), 7.60 (1H, dd, J=7Hz,2Hz), 7.53 (1H, td, J=2Hz,8Hz), 7.44 (1H, d, J=7Hz), 7.38 (1H, td, J=2Hz,8Hz), 7.18 (1H, d, J=8Hz), 7.03 (1H, td, J=2Hz,7Hz), 6.96 (1H, td, J=2Hz,8Hz), 6.91 (1H, s), 5.42 (1H, dd, J=7Hz,5Hz), 5.23 (1H, dd, J=10Hz,6Hz), 3.41 (1H, dd, J=8Hz,7Hz), 3.29 (3H, s), 3.57 (3H, s), 1.70 (2H, m), 1.44 (1H, m), 0.90 (3H, s), 0.89 (3H, s). MS (DCI/NH_3) m/e 558 $(M+H)^+$, 575 $(M+H+NH_3)^+$. Anal calc for $C_{31}H_{31}N_3O_7$. 0.4TFA: C, 63.32; H, 5.25; N, 6.97. Found: C, 63.33; H, 5.33; N, 6.69.

Example 23

2-{(1R)-1-(N-(2S)-(2-(1-Isoquinolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared using the procedures described in Example 20, substituting isoquinoline-1-carboxylic acid for 1-naphthoic acid in Example 20A. ^{1}H NMR (300 MHz, CD_3OD) δ 8.66 (1H, d, J=9Hz), 8.42 (1H, d, J=7Hz), 8.07 (1H, d, J=9Hz), 8.00 (1H, d, J=7Hz), 7.85 (1H, td, J=2Hz,8Hz), 7.73 (1H, td, J=2Hz,7Hz), 7.39 (1H, d, J=9Hz), 7.07 (1H, d, J=9Hz), 6.98 (1H, td, J=2Hz,7Hz), 6.88 (1H, td, J=2Hz,7Hz), 6.85 (1H, s), 5.50 (1H, dd, J=7Hz,5Hz), 5.40 (1H, dd, J=8Hz,6Hz), 3.51 (3H, s), 3.41 (1H, dd, J=8Hz,7Hz), 2.59 (3H, s), 1.8 (2H, m), 1.62 (2H, m), 0.93 (3H, d, J=7Hz), 0.88 (3H, d, J=7Hz). MS (DCI/NH_3) m/e 569 $(M+H)^+$. Anal calc for $C_{31}H_{32}N_4O_6 \cdot 4H_2O$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.88; H, 5.81; N, 8.33.

Example 24

2-{(1R)-1-(N-(2S)-(2-(Cyclohexylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 20, substituting cyclohexylacetic acid for 1-naphthoic acid in Example 20A. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.52 (1H, d, J=8Hz), 7.28 (1H, d, J=8Hz), 7.13 (1H, td, J=2Hz,8Hz), 7.01 (1H, d, J=2Hz,8Hz), 6.93 (1H, s), 5.38 (1H, dd, 7Hz, 5Hz), 4.96 (1H, dd, 9Hz,7Hz), 3.74 (3H, s), 3.40 (1H, dd, 8Hz,7Hz), 2.54 (3H, s), 2.18 (2H, m), 1.6 (6H, m), 1.46 (2H, m), 1.20 (4H, m), 1.20 (4H, m), 0.91 (3H, d, J=7Hz), 0.90 (1H, d, J=7Hz). MS (DCI/NH_3) m/e 538 $(M+H)^+$, 555 $(M+H+NH_3)^+$. Anal calc for $C_{30}H_{39}N_3O_6 \cdot 0.5$ TFA: C, 62.62; H, 6.70; N, 7.07. Found: C, 62.18; H, 6.90; N, 6.80.

Example 25

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

Example 25A

2-((1R)-1-(Fmoc-Amino-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-imidazole-4-carboxylic acid benzyl ester

N-(Diphenylmethylene)glycine benzyl ester (4.1 g) was dissolved in THF (25 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (12.5 mL, 1 N solution in THF) was added slowly over 10 minutes, and the resulting yellow slurry was stirred at -78 °C for 30 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (0.93 mL) in THF (25 mL) at -78 °C. After the addition was complete, the reaction was allowed to warm to room temperature and stirring was continued for four hours. The reaction was then quenched with 2 N HCl (15 mL). The THF was evaporated and the resulting aqueous solution was washed with EtOAc (2 x 50 mL). The organic phases were discarded and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (100 mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine benzyl ester hydrochloride as a yellow solid which was used without further purification.

Fmoc-D-(1-Methyl)-Tryptophan (5.75 g), prepared by the method of Cook, et al., Chem. Pharm. Bull. 13 88 (1965), was dissolved in THF (20 mL) and the solution cooled to -20 °C. N-Methylmorpholine (1.45 mL) was added followed by the dropwise addition of isobutylchloroformate (1.7 mL). After the addition was complete, the reaction was stirred for 30 minutes at -20 °C at which time the bath was removed. The 2-acetylglycine ester from above was dissolved in DMF (20 mL) and added to the mixed anhydride. N-Methylmorpholine (1.45 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (75 mL) was added and the layers separated. The organic layer was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel eluting with 15% EtOAc/hexane to give the product as a yellow solid (3.85 g, 49% yield for the two steps).

Example 25B

2-[(1R)-1-(Fmoc-Amino)-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid benzyl ester

The compound resulting from Example 25A (5.0 g) was dissolved in acetic acid (25 mL). Ammonium acetate (4.0 g) was added and the mixture heated at reflux for 16 hours. After cooling, the solvent was evaporated under reduced pressure and the residue taken up in saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The resulting orange oil was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexane to afford 1.10 g (23%) of the title compound.

Example 25C

2-[(1R)-1-Amino-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid benzyl ester

The compound resulting from Example 25B (100 mg) was suspended in 3 mL of THF. Piperidine (0.3 mL) was added and the resulting solution was stirred at ambient temperature for 45 minutes. The solvents were removed *in vacuo*, and the residue was triturated with hexanes, filtered, and dried under high vacuum for 15 minutes to afford 63 mg (100% yield) of the title compound.

Example 25D

(2S)-2-(N-Cyclohexylaminocarboxy)isovaleric acid

The title compound was prepared according to the procedures described in Example 1F, substituting cyclohexylamine for N-methylcyclohexylamine.

Example 25E

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid benzyl ester

To the compound resulting from Example 25C combined with 80 mg of the compound resulting from Example 25D in 3 mL of THF and 3 mL of DMF were added sequentially 42 mg of HOBt, 8 drops of N-methyl morpholine, and 57 mg of EDCI. The resultant solution was stirred overnight at ambient temperature, the solvents were removed *in vacuo*, and the residue was taken up in EtOAc. The resulting solution was washed sequentially with 1:1 sodium

bicarbonate solution/water, 1 N H_3PO_4 and brine, dried over Na_2SO_4, filtered through Celite®, and concentrated *in vacuo* to give the title compound as a yellowish oil.

Example 25F

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The compound resulting from Example 25E was dissolved in 15 mL of ethanol, 30 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The crude material was purified by trituration with ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (43.5 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 6H, J=7Hz), 1.1-1.9 (m, 13H), 2.50 (s, 3H), 3.3-3.5 (m, 4H), 3.76 (s, 3H), 5.34 (dd, 1H, J=7Hz,8Hz), 7.03 (s, 1H), 7.04 (dt, 1H, J=1Hz,8Hz), 7.17 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.34 (d, 1H, J=8Hz), 7.43 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 538 $(M+H)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.2$ TFA: C, 55.92; H, 6.01; N, 10.38. Found: C, 55.90; H, 5.99; N, 10.34.

Example 26

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

Example 26A

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid benzyl ester

The title compound was prepared according to the procedures described in Example 25E, substituting the compound of Example 17A for the compound of Example 25D.

Example 26B

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-imidazole-4-carboxylic acid

The compound resulting from Example 26A was reacted according to the procedure of Example 25F. The crude material was triturated with ether; the resultant material was purified by reverse phase HPLC eluting with a gradient of 0 to 80% acetonitrile in 0.1% TFA. The appropriate fraction was lyophilized to give the title compound as a white solid (17 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.59 (d, 3H, J=6Hz), 0.61 (d, 3H, J=6Hz), 0.79 (m, 1H), 0.96 (ddd, 1H, J=5Hz,10Hz,14Hz), 1.1-1.4 (m, 6H), 1.6-1.9 (m, 5H), 2.25 (dd, 1H, J=3Hz,15Hz), 2.50 (dd, 1H, J=14Hz,15Hz), 2.56 (s, 3H), 2.63 (m, 1H), 3.2-3.4 (m, 2H), 3.65 (m, 1H), 3.77 (s, 3H), 5.52 (dd, 1H, J=5Hz,11Hz), 7.04 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.08 (s, 1H), 7.18 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.35 (d, 1H, J=8Hz), 7.55 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 536 $(M+H)^+$. Anal calcd for $C_{30}H_{41}N_5O_4 \cdot 3.0$ TFA: C, 49.26; H, 5.05; N, 7.98. Found: C, 49.14; H, 5.33; N, 8.33.

Example 27A

2-{(1R)-1-(N-(2S)-(2-hydroxyisovaleryl)-amino)-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid

The compound resulting from 1B (1.17g, 2.39mmol) was dissolved in 4N hydrochloric acid / dioxane and stirred for 30 minutes. The volatiles were removed in vacuo and the residue was suspended in DMF (7mL), and to this was added successively NMM (0.26mL, 2.39mmol, 1eq), HOBt (355mg, 2.63mmol, 1.1eq), leucic acid (315mg, 2.39mmol, 1eq) and EDCI (600mg, 3.11mmol, 1.3eq). The mixture was stirred overnight at room temperature, then partitioned between water and ethyl acetate. The organic solution was washed with saturated sodium bicarbonate solution, 1N phosphoric acid, water, and brine, dried and evaporated to give the crude product which was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate/hexanes.

Example 27B

2-{(1R)-1-(N-(2S)-(2-(Phenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

To a stirred solution of the product of Example 27A (71 mg, 0.14 mmol) in DMF (1 mL) was added successively phenylacetic acid (19 mg, 0.14 mmol, 1 eq), HOBt (21 mg, 0.15 mmol, 1.1 eq), DMAP (2 mg) and EDCI (35 mg, 0.18 mmol, 1.3 eq). The mixture was stirred 48 hours, then poured into ethyl acetate and washed successively with saturated aqueous sodium bicarbonate solution, 1 N phosphoric acid, water, and saturated aqueous sodium chloride solution. The organic solution was dried over Na_2SO_4, filtered and evaporated to yield an oil which was purified by flash chromatography on silica gel eluting with 35% ethyl acetate in hexanes to afford the diester.

This compound was dissolved in ethyl acetate and hydrogenated at 1 atmosphere of H_2 over 10% palladium on charcoal. The catalyst was removed by filtration through a pad of Celite®, and the solvent was then removed under vacuum to yield the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, d, J=8Hz), 7.3-7.14 (6H, m), 7.09 (2H, m), 6.76 (1H, s), 5.48 (1H, q, J=7Hz), 5.17 (1H, dd, J=8Hz, 3Hz), 3.70 (3H, s), 3.46 (2H, s), 3.32 (2H, m), 2.54 (3H,s), 1.63 (2H, m), 1.51 (3H, m), 0.79 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz). MS (FAB, NBA,CH_2Cl_2) m/e 532 $(M+H)^+$, 554 $(M+NH_4)^+$. Anal.calc. for $C_{30}H_{33}N_3O_6 \cdot 0.5\ H_2O$: C, 66.65; H, 6.34; N, 7.77. Found: C, 66.35; H, 6.34; N, 7.57.

Example 28

2-{(1R)-1-(N-(2S)-(2-(2-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 27B except o-fluorophenylacetic acid was substituted for phenylacetic acid. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.50 (1H, d, J=8Hz), 7.31 (1H, d, J=8Hz), 7.29-7.00 (6H, m), 6.93 (1H, s), 5.39 (1H, dd, J=9Hz, 7Hz), 4.97 (1H, dd, J=9Hz, 3Hz), 3.72 (3H, s), 3.69, (2H, m), 3.42 (1H, dd, J=15Hz, 6Hz), 2.54 (3H,s), 1.54 (2H, m), 1.33 (3H, m), 0.79 (3H, d, J=7Hz), 0.77 (3H,

d, J=7Hz). MS (DCI/NH_3) m/e 550 $(M+H)^+$. Anal.calc. for $C_{30}H_{32}FN_3O_6 \cdot 0.4$ TFA: C, 62.16; H, 5.49; N, 7.06. Found: C, 62.15; H, 5.45; N, 7.01.

Example 29

2-{(1R)-1-(N-(2S)-(2-(3-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 27B except m-fluorophenylacetic acid was substituted for phenylacetic acid. ^1H NMR (300 MHz, CD_3OD) δ 7.48 (1H, d, J=8Hz), 7.31 (1H, d, J=8Hz), 7.29-7.00 (6H, m), 6.93 (1H, s), 5.38 (1H, dd, J=9Hz, 7Hz), 4.95 (1H, dd, J=9Hz, 4Hz), 3.72 (3H, s), 3.69, (2H, m), 3.42 (1H, dd, J=15Hz, 6Hz), 2.54 (3H,s), 1.54 (2H, m), 1.33 (3H, m), 0.79 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz). MS (FAB, NBA,CH_2Cl_2) m/e 550 $(M+H)^+$, 572 $(M+Na)^+$. HRMS: Calc. for $C_{30}H_{32}FN_3O_6$: 550.2353. Found: 550.2357.

Example 30

2-{(1R)-1-(N-(2S)-(2-(4-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 27B except p-fluorophenylacetic acid was substituted for phenylacetic acid. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^1H NMR (300 MHz, CD_3OD) δ 7.48 (1H, d, J=8Hz), 7.35 (1H, d, J=8Hz), 7.18 (3H, m), 7.00 (4H, m), 5.39 (1H, dd, J=9Hz, 7Hz), 4.95 (1H, dd, J=9Hz, 4Hz), 3.72 (3H, s), 3.69, (2H, m), 3.42 (1H, dd, J=15Hz, 6Hz), 2.54 (3H,s), 1.54 (2H, m), 1.33 (3H, m), 0.79 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz). MS (DCI/NH_3) m/e 550 $(M+H)^+$, 567 $(M+NH_4)^+$. Anal.calc. for $C_{30}H_{32}FN_3O_6 \cdot 1.2$ TFA: C, 56.70; H, 4.88; N, 6.12. Found: C, 56.78; H, 5.24; N, 5.75.

Example 31

2-{(1R)-1-(N-(2S)-(2-(2-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 27B except o-methylphenylacetic acid was substituted for phenylacetic acid. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.35 (1H, d, J=8Hz), 7.48 (1H, d, J=8Hz), 7.30 (1H, d, J=8Hz), 7.10 (4H, m), 7.02 (1H, td, 9Hz, 1Hz), 6.91 (1H, s), 5.35 (1H, dd, J=9Hz, 7Hz), 4.95 (1H, dd, J=9Hz, 4Hz), 3.72 (3H, s), 3.69, (2H, m), 3.42 (1H, dd, J=15Hz, 6Hz), 2.54 (3H,s), 2.10 (3H, s), 1.54 (2H, m), 1.33 (3H, m), 0.79 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz). MS (DCI/NH_3) m/e 546 $(M+H)^+$, 563 $(M+NH_4)^+$.
Anal.calc. for $C_{31}H_{35}N_3O_6 \cdot 1.1$ TFA: C, 59.43; H, 5.42; N, 6.26. Found: C, 59.63; H, 5.58; N, 6.31.

Example 32

2-{(1R)-1-(N-(2S)-(2-(3-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 27B except m-methylphenylacetic acid was substituted for phenylacetic acid. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.49 (1H, d, J=8Hz), 7.30 (1H, d, J=8Hz), 7.10 (3H, m), 7.02 (3H, m), 6.91 (1H, s), 5.35 (1H, dd, J=9Hz, 7Hz), 4.95 (1H, dd, J=9Hz, 4Hz), 3.72 (3H, s), 3.69, (2H, m), 3.42 (1H, dd, J=15Hz, 6Hz), 2.54 (3H,s), 2.15 (3H, s), 1.54 (2H, m), 1.33 (3H, m), 0.79 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz). MS (DCI/NH_3) m/e 546 $(M+H)^+$.
Anal.calc. for $C_{31}H_{35}N_3O_6 \cdot 0.3$ TFA: C, 65.46; H, 6.14; N, 7.25. Found: C, 65.38; H, 6.10; N, 7.22.

Example 33

2-{(1R)-1-(N-(2S)-(2-(4-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 27B except p-methylphenylacetic acid was substituted for phenylacetic acid. The product was dissolved in acetonitrile and 0.1% TFA and

lyophilized to give a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.30 (1H, d, J=8Hz), 7.44 (1H, d, J=8Hz), 7.30 (1H, d, J=8Hz), 7.15 (1H, td, J=7Hz, 1Hz), 7.09 (3H, m), 7.02 (1H, td, 9Hz, 1Hz), 6.91 (1H, s), 5.35 (1H, dd, J=9Hz, 7Hz), 4.95 (1H, dd, J=9Hz, 4Hz), 3.72 (3H, s), 3.69, (2H, m), 3.42 (1H, dd, J=15Hz, 6Hz), 2.54 (3H,s), 2.10 (3H, s), 1.54 (2H, m), 1.33 (3H, m), 0.79 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz). MS (DCI/NH_3) m/e 546 $(M+H)^+$, 563 $(M+H+NH_3)^+$. Anal.calc. for $C_{31}H_{35}N_3O_6 \cdot 1.1$ TFA: C, 59.43; H, 5.42; N, 6.26. Found: C, 59.26; H, 5.52; N, 5.91.

Example 34

2-{(1R)-1-(N-(2S)-(2-(3-Quinolinylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 20 except 3-quinolinecarboxylic acid was substituted for 1-naphthylenecarboxylic acid in Example 20A. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^{1}H NMR ((300 MHz, CD_3OD, $CDCl_3$) δ 9.30 (1H, d, J=3Hz), 8.87 (1H, d, J=3Hz), 8.14 (1H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 7.92 (1H, dt, J=7Hz, 2Hz), 7.72 (1H, dt, J=7Hz, 2Hz), 7.39 (1H, d, J=8Hz), 7.08 (1H, d, J=8Hz), 6.97 (1H, dt, J=7Hz, 2Hz), 6.89 (1H, dt, J=7Hz, 2Hz), 6.82 (1H, s), 5.50 (1H, dd, J=10Hz, 6Hz), 5.37 (1H, dd, J=10Hz, 4Hz), 3.59 (3H, s), 3.40 (2H, m), 2.60 (3H,s), 1.86 (1H, m), 1.71 (1H, m), 1.57 (1H, m), 0.93 (3H, d, J=3Hz), 0.90 (3H, d, J=3Hz). MS (FAB) m/e 569 $(M+H)^+$. Anal.calc. for $C_{32}H_{32}N_4O_6 \cdot 0.15$ TFA: C, 66.23; H, 5.53; N, 9.57. Found: C, 66.41; H, 5.82; N, 9.44.

Example 35

2-{(1R)-1-(N-(2S)-(2-((2S)-(+)-2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 20 except (2S)-(+)-2-phenylpropionic acid was substituted for 1-naphthylenecarboxylic acid in Example 20A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, m), 7.25-7.05 (7H, m), 7.02 (1H, m), 6.77 (1H, m), 5.27 (1H, m), 5.15 (1H, m), 3.63 (3H, s), 3.25 (1H, m), 3.06 (1H, m), 2.50 (3H, s), 1.70-145 (3H, m), 1.40 (3H, d, J=8Hz), 0.90 (1H, m), 0.75 (3H, d, J=7Hz), 0.67 (3H, d, J=7Hz). MS

(DCI/NH_3) m/e546 $(M+H)^+$, 563 $(M+H+NH_3)^+$. Anal.calc. for $C_{31}H_{35}N_3O_6 \cdot 2.50\ H_2O$: C, 63.04; H, 6.83; N, 7.11. Found: C, 62.98; H, 6.44; N, 6.94.

Example 36

2-{(1R)-1-(N-(2S)-(2-(2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 20 except 2-phenylpropionic acid was substituted for 1-naphthylenecarboxylic acid in Example 20A. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (1H, m), 7.25-7.05 (7H, m), 7.03 (1H, m), 6.81 (1H, m), 5.30 (1H, m), 5.10 (1H, m), 3.62 (3H, bd, J=8Hz), 3.23 (1H, m), 3.08 (1H, m), 2.50 (3H, bs), 1.70-145 (3H, m), 1.41 (bd, J=8Hz) and 1.32 (bd, J=8Hz) total of 3H, 0.90 (1H, m), 0.73 (m), 0.67 (m), 0.62 (m), and 0.50 (m) total of 6H. MS (FAB) m/e 568 $(M+Na)^+$, 590 $(M+2Na-H)^+$. Anal.calc. for $C_{31}H_{35}N_3O_6 \cdot 1.30\ H_2O \cdot 0.50$ TFA: C, 61.39; H, 6.13; N, 6.71. Found: C, 61.40; H, 6.17; N, 6.70.

Example 37

2-{(1R)-1-(N-(2S)-(2-(2,6-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 20 except 2,6-difluorophenylacetic acid was substituted for 1-naphthylenecarboxylic acid in Example 20A. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, bd, J=10Hz), 7.25-7.10 (3H, m), 7.05 (1H, m), 6.80 (3H, m), 5.35 (1H, m), 5.15 (1H, m), 3.63 (3H, s), 3.58 (2H, bs), 3.29 (2H, m), 2.54 (3H, s), 1.66 (1H, m), 1.50 (2H, m), 0.80 (3H, d, J=7Hz), 0.72 (3H, d, J=7Hz). MS (DCI/NH_3) m/e 568 $(M+H)^+$, 585 $(M+H+NH_3)^+$. Anal.calc. for $C_{30}H_{31}F_2N_3O_6 \cdot 1.00\ H_2O$: C, 61.53; H, 5.68; N, 7.18. Found: C, 61.21; H, 5.44; N, 6.91.

Example 38

2-{(1R)-1-(N-(2S)-(2-(2,4-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 20 except 2,4-difluorophenylacetic acid was substituted for 1-naphthylenecarboxylic acid in Example 20A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, J=8Hz), 7.30-7.15 (2H, m), 7.10-6.95 (2H, m), 6.80 (1H, s), 6.72 (2H, m), 5.32 (1H, m), 5.15 (1H, dd, J=8Hz, 3Hz), 3.69 (3H, s), 3.45 (2H, bs), 3.39 (2H, d, J=8Hz), 2.55 (3H, s), 1.64 (1H, m), 1.52 (2H, m), 0.82 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz). MS (DCI/NH_3) m/e 568 $(M+H)^+$, 585 $(M+H+NH_3)^+$. Anal.calc. for $C_{30}H_{31}F_2N_3O_6 \cdot 0.50\ H_2O$: C, 62.49; H, 5.59; N, 7.29. Found: C, 62.48; H, 5.55; N, 7.19.

Example 39

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-ethyl-oxazole-4-carboxylic acid

Example 39A

D-(1-Methyl)-Tryptophanyl-(2-propionyl-glycine)-benzyl ester

The title compound was prepared by the methods described in Examples 1A-1C, substituting propionyl chloride for acetyl chloride in Example 1A.

Example 39B

2-{(1R)-1-1(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-ethyl-oxazole-4-carboxylic acid

The compound resulting from Example 39A was coupled with the compound resulting from Example 1F by the method described by in Example 1G, and the benzyl ester protecting group was removed as in Example 1H. The crude product was triturated with 1:1 ethyl ether-hexane, dissolved in acetonitrile and water, and lyophilized to give the title compound as a white solid. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^{1}H NMR ($CDCl_3$-CD_3OD, 300 MHz) δ 0.88 (d, 6H, J-8Hz), 1.13 (t, 3H, J=8Hz), 1.2-1.5 (m, 8H), 1.63 (m, 3H), 1.80 (m, 2H), 2.75 (br s, 3H),

2.95 (dq, 2H, J= 1,8Hz), 3.38 (d, 2H, J=8Hz), 3.74 (s, 3H), 3.83 (br s, 1H), 5.0 (dd, 1H, J=5,9Hz), 5.43 (dt, 1H, J=1,8Hz), 6.85 (br s, 1H), 7.03 (dt, 1H, J=1,8Hz), 7.15 (dt, 1H, J=1,8Hz), 7.28 (d, 1H, J=8Hz), 7.40 (d, 1H, J=8Hz). MS (FAB) m/e 567 $(M+H)^+$, 589 $(M+Na)^+$, 605 $(M+K)^+$. Anal calcd for $C_{31}H_{42}N_4O_6 \cdot 0.25$ TFA: C, 63.57; H, 7.15; N, 9.41. Found: C, 63.64; H, 7.22; N, 9.77.

Example 40

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid

The compound resulting from Example 39A was coupled with the compound resulting from Example 1F (but substituting N-methylaniline for N-methylcyclohexylamine) by the method described by in Example 1G and the benzyl ester removed as in Example 1H. The crude product was triturated with 1:1 ethyl ether/ hexane, dissolved in acetonitrile and water, and lyophilized to give a white solid. ^1H NMR ($CDCl_3/CD_3OD$, 300 MHz) δ 0.80 (m, 6H), 1.42 (m, 1H), 1.55 (m, 2H), 2.95 (dq, 2H, J=1,8Hz), 3.22 (s, 3H), 3.40 (d, 2H, J=8Hz), 3.70 (s, 3H), 5.05 (dd, 1H, J=4,9Hz), 5.42 (t, 1H, J=8Hz), 6.86 (s, 1H), 7.05 (m, 3H), 7.25 (m, 5H), 7.42 (d, 1H, J=8Hz). MS (FAB) m/e 561 $(M+H)^+$, 583 $(M+Na)^+$, 599 $(M+K)^+$. Anal calcd for $C_{31}H_{36}N_4O_6 \cdot 3.5\ H_2O$, 0.4 TFA: C, 57.07; H, 6.54; N, 8.37. Found: C, 57.22; H, 6.55; N, 8.49.

Example 41

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid (4-isopropylbenzenesulfonyl)carboxamide

The compound resulting from Example 6 (60 mg) was dissolved in 3 mL of THF, 30 mg of carbonyldiimidazole (CDI) was added, and the resultant solution was stirred at ambient temperature for 3 hours. 4-Isopropylbenzenesulfonamide (24 mg) and DBU (3 drops) were added, and stirring was continued for 20 hours. The solvents were removed *in vacuo*, and the residue was purified by preparative HPLC (Vydac μC18) eluting with a 20-90% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (32 mg). ^1H NMR (CD_3OD, 300 MHz) of major rotamer δ 0.77 (broadened, 6H), 1.2-1.5 (m, 3H), 1.28 (d, 6H, J=7),

2.47 (s, 3H), 3.03 (m, 1H), 3.22 (bd s, 3H), 3.3-3.5 (m, 2H), 3.72 (s, 3H), 4.88 (dd, 1H, J=5,10), 5.36 (dd, 1H, J=7,8), 6.95 (s, 1H), 7.01 (dt, 1H, J=1,7), 7.1-7.3 (m, 7H), 7.45 (d, 2H, J=8); 7.47 (m, 1H), 7.97 (d, 2H, J=8). MS (FAB/NBA) m/e 728 $(M+H)^+$. Anal calcd for $C_{39}H_{45}N_5O_7S \cdot 0.5$ TFA: C, 61.21; H, 5.84; N, 8.92. Found: C, 61.46; H, 6.18; N, 8.67.

Example 42

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid (methanesulfonyl)carboxamide

The title compound was prepared by the procedures described in Example 41 substituting methanesulfonamide for isopropylbenzenesulfonamide. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^1H NMR (CD_3OD, 300 MHz) of major rotamer δ 0.76 (broadened, 6H), 1.2-1.5 (m, 3H), 2.58 (s, 3H),3.22 (bd s, 3H), 3.30 (s, 3H); 3.3-3.5 (m, 2H), 3.72 (s, 3H), 4.90 (dd, 1H, J=5,10), 5.39 (m, 1H), 6.96 (s, 1H), 7.05 (dt, 1H, J=1,7), 7.1-7.3 (m, 7H), 7.47 (d, 1H, J=8). MS (DCI/NH_3) m/e 624 $(M+H)^+$, 641 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{37}N_5O_7S \cdot 0.4$ TFA: C, 57.07; H, 5.63; N, 10.46. Found: C, 56.91; H, 5.66; N, 10.21.

Example 43

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole

Example 43A

2-{(1R)-1-(Boc-Amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carbonitrile

The compound resulting from Example 1B (3.00 g) was dissolved in 50 mL of ethanol, 100 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite, and the solvents were removed *in vacuo*. The crude acid was dissolved in 40 mL of THF; 1.2 mL of N-methylmorpholine was added, and the solution was cooled to 0 °C. Iso-

butylchloroformate (0.9 mL) was added streamwise, and the resultant mixture was stirred at 0 °C for 45 minutes. Aqueous ammonia (3 mL of a 30% solution) was added, and the mixture was warmed to ambient temperature over one hour. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with saturated sodium bicarbonate solution, 1 N aqueous H_3PO_4, and brine, dried and concentrated *in vacuo*. The crude amide thus obtained was dissolved in 30 mL of pyridine and cooled to 0 °C; phosphorus oxychloride (1.2 mL) was added, the resultant mixture was allowed to warm to ambient temperature and stirred for 6 hours. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with saturated sodium bicarbonate solution, 1 N aqueous H_3PO_4, and brine, dried and concentrated *in vacuo*. The product (1.54 g, 67% overall yield) was isolated by flash chromatography on silica gel, eluting with a gradient of 30% going to 50% EtOAc in hexanes.

Example 43B

2-{(1R)-1-(Amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carbonitrile

The compound resulting from Example 43A (750 mg) was dissolved in 20 mL of TFA and stirred at ambient temperature for 90 minutes. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with saturated sodium bicarbonate solution and brine, dried and concentrated *in vacuo*.

Example 43C

2-{(1R)-1-(N-(2S)-[2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl]-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carbonitrile

The compound resulting from Example 43B was combined in 10 mL of THF and 3 mL of DMF with 550 mg of the compound resulting from Example 1F, 270 mg of HOBt, and 0.5 mL of NMM; 385 mg of EDCI was added, and the solution was stirred for 15 hours at ambient temperature. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with saturated sodium bicarbonate solution, 1 N aqueous H_3PO_4, and brine,

dried, and concentrated *in vacuo*. The product (773 mg, 73% yield) was isolated by flash chromatography on silica gel, eluting with a step gradient of 28% going to 33% going to 40% EtOAc in hexanes.

Example 43D

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole

The compound resulting from Example 43C (50 mg) was combined with 20 mg of hydroxylamine hydrochloride in 1 mL of ethanol, 1 drop of 1 N ethanolic sodium ethoxide was added, and the mixture was heated at 80 °C for 3 hours. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with bicarb and brine, dried, and concentrated *in vacuo*. The resultant crude hydroxyamidine was dissolved in 1.5 mL of THF; 25 mg of CDI was added, followed by 1 drop of DBU. The solution was stirred for 16 hours at ambient temperature. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with 1N aqueous H_3PO_4 and brine, dried and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (13 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 6H, J=7Hz), 1.1-1.8 (m, 13H), 2.52 (s, 3H), 2.75 (bd s, 3H), 3.3-3.5 (m, 2H), 3.74 (s, 3H), 3.82 (m, 1H), 4.86 (m, 1H), 5.42 (dd, 1H, J=7Hz,9Hz), 6.97 (s, 1H), 7.03 (dt, 1H, J=1Hz,7Hz), 7.15 (dt, 1H, J=1Hz,7Hz), 7.31 (d, 1H, J=7Hz), 7.48 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 593 $(M+H)^+$, 610 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{40}N_6O_6 \cdot 1.1$ TFA: C, 55.53; H, 5.77; N, 11.70. Found: C, 55.47; H, 5.84; N, 11.99.

Example 44

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole

Example 44A

2-{(1R)-1-(N-(2S)-[2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl]-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carbonitrile

(2S)-2-(N-Phenyl-N-methylaminocarboxy)isovaleric acid (made by the method described in Example 1F, but substituting N-methylaniline for N-methylcyclohexylamine) was coupled with the compound resulting from Example 43B by the method described in Example 43C.

Example 44B

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole

The compound resulting from Example 44A was converted to the title compound by the procedure in Example 43D. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.77 (broadened, 6H), 1.2-1.5 (m, 3H), 2.53 (s, 3H), 3.22 (s, 3H), 3.3-3.5 (m, 2H), 3.72 (s, 3H), 4.91 (dd, 1H, J=5Hz, 10Hz), 5.43 (dd, 1H, J=7Hz,8Hz), 6.97 (s, 1H), 7.04 (ddd, 1H, J=1Hz, 7Hz, 8Hz), 7.1-7.3 (m, 7H), 7.47 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 593 $(M+H)^+$, 610 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{34}N_6O_6 \cdot 0.2$ TFA: C, 61.88; H, 5.66; N, 13.79. Found: C, 62.07; H, 5.70; N, 13.54.

Example 45

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-4-(5-tetrazolyl)oxazole

The carbonitrile resulting from Example 43C (100 mg) was combined with 50 mg of sodium azide in 1 mL of toluene, 150 μL of trimethyltin chloride was added, and the sealed reaction vessel was heated at 145 °C for 6 hours. The reaction was quenched by the addition of 0.5 mL of methanol followed by 1 mL of 1 N aqueous H_3PO_4, the mixture was concentrated *in vacuo*, the residue was taken up in EtOAc and washed with 1 N aqueous H_3PO_4. The product (113 mg) was isolated by flash chromatography on silica gel, eluting with a step gradient of EtOAc going to 10% CH_3OH in EtOAc. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 6H, J=7Hz), 1.0-1.8 (m, 13H), 2.68 (s, 3H), 2.75

(bd s, 3H), 3.3-3.5 (m, 2H), 3.74 (s, 3H), 3.82 (m, 1H), 4.88 (m, 1H), 5.46 (dd, 1H, J=7Hz,9Hz), 6.99 (s, 1H), 7.01 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.15 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.30 (d, 1H, J=7Hz), 7.50 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 577 $(M+H)^+$, 594 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{40}N_8O_4 \cdot 1.8$ TFA: C, 51.61, H, 5.39; N, 14.33. Found: C, 51.62; H, 5.44; N, 14.69.

Example 46

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(5-tetrazolyl)oxazole

The title compound was prepared according to the procedures described in Example 45, but substituting the compound from Example 44A for the compound from Example 43C. The product was dissolved in acetonitrile and 0.1% TFA and lyophilized to give a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.77 (broadened, 6H), 1.2-1.5 (m, 3H), 2.67 (s, 3H), 3.21 (s, 3H), 3.3-3.5 (m, 2H), 3.71 (s, 3H), 4.93 (dd, 1H, J=5Hz,10Hz), 5.46 (dd, 1H, J=7Hz,8Hz), 6.98 (s, 1H), 7.03 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.1-7.3 (m, 7H), 7.48 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 571 $(M+H)^+$, 588 $(M+H+NH_3)^+$. Anal calcd for $C_{30}H_{34}N_8O_4 \cdot 2.0$ TFA: C, 51.13; H, 4.54; N, 14.03. Found: C, 50.84; H, 4.54; N, 14.49.

Example 47

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 25, but substituting the compound prepared in Example 1F for the compound from Example 25D. ^1H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J=7Hz), 0.84 (d, 3H, J=7Hz), 1.0-1.9 (m, 13H), 2.50 (s, 3H), 2.78 (bd s, 3H), 3.3-3.6 (m, 2H), 3.75 (s, 3H), 3.88 (m, 1H), 4.75 (dd, 1H, J=5Hz, 8Hz), 5.34 (dd, 1H, J=7Hz,9Hz), 7.02 (s, 1H), 7.04 (ddd, 1H, J=1Hz, 7Hz, 8Hz), 7.17 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.34 (d, 1H, J=7Hz), 7.47 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$. HRMS calcd for $C_{30}H_{42}N_5O_5$: 552.3186. Found: 552.3172.

Example 48

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 25, but substituting (2S)-2-(N-phenyl-N-methylaminocarboxy)isovaleric acid for the compound from Example 25D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.76 (broadened, 6H), 1.2-1.5 (m, 3H), 2.42 (broad s, 3H), 3.26 (s, 3H), 3.3-3.5 (m, 2H), 3.64 (s, 3H), 4.95 (m, 1H), 5.33 (dd, 1H, J=7Hz,9Hz), 6.98 (s, 1H), 7.04 (ddd, 1H, J=1Hz,7Hz.8Hz), 7.16 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.2-7.4 (m, 6H), 7.47 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 546 $(M+H)^+$. HRMS calcd for $C_{30}H_{36}N_5O_5$: 546.2716. Found: 546.2733.

Example 49

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-thiazole-4-carboxylic acid

Example 49A

Cbz-D-(1-Methyl-tryptophanyl)-(2-acetylGlycine) ethyl ester

N-(Diphenylmethylene)glycine ethyl ester (30.0 g) was dissolved in THF (125 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (100 mL, 1 N solution in THF) was added slowly over 10 minutes, and the resulting yellow slurry was stirred at -78 °C for 45 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (8.4 mL) in THF (50 mL) at -78 °C. Additional THF (250 mL) was added to the anion solution to facilitate transfer to the acetyl chloride solution. Complete transfer of the anion took about 2.5 hours. After the addition was complete, the reaction was allowed to warm to room temperature and stirring was continued for four hours. The reaction was then quenched with 2 N HCl (115 mL). The THF was evaporated and the resulting aqueous solution was washed with EtOAc (2 x 100 mL). The organic phases were discarded and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (150 mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine ethyl ester hydrochloride as a yellow solid which was used without further purification.

Cbz-D-1-Methyl-Tryptophan (42.5 g) was dissolved in THF (100 mL) and the solution cooled to -20 °C. N-Methylmorpholine (13 mL) was added followed by the dropwise addition of isobutylchloroformate (15.6 mL). After the addition was complete, the reaction was stirred for 30 minutes at -20 °C at which time the bath was removed. The 2-acetylglycine ester from above was dissolved in DMF (50 mL) and added to the mixed anhydride. N-Methylmorpholine (13 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (200 mL) was added and the layers separated. The organic layer was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel eluting with 15% EtOAc-hexane. The title compound was isolated as an orange oil (31.2 g, 58% yield for the two steps).

Example 49B

2-[(1R)-(Cbz-Amino)-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-thiazole-4-carboxylic acid ethyl ester

The compound above (0.335 g) was dissolved in THF (5 mL). Lawesson's reagent (0.45 g) was added and the mixture stirred at reflux for five hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (20 mL). The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$ and evaporated under reduced pressure to give a yellow oil which was purified by flash chromatography eluting with 15% EtOAc-hexane to give the product as a white solid (155 mg, 46%).

Example 49C

2-[(1R)-1-[N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-thiazole-4-carboxylic acid

The above thiazole (72 mg, 0.15 mmol) was dissolved in 2 mL of 30% HBr in HOAc and stirred at ambient temperature for 3 hours. The solvents were removed *in vacuo*, the residue was taken up in saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were

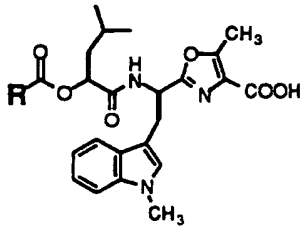
washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo*. The crude amine (65 mg) was dissolved in THF (2 mL). HOBt (30 mg), (2S)-2-(N-cyclohexyl-N-methylaminocarboxy)isovaleric acid (55 mg) and EDCI (42 mg) were added. N-Methylmorpholine (10 μL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane.

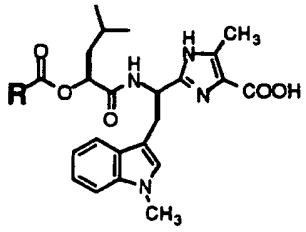
The product was dissolved in THF (2 mL), a solution of LiOH (50 mg) in H_2O (1 mL) was added and the mixture warmed at 80 °C for 10 hours. The solvents were evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J=7Hz), 0.83 (d, 3H, J=7Hz), 1.0-1.9 (m, 13H), 2.69 (s, 3H), 2.76 (bd s, 3H), 3.30 (m,1H), 3.52 (dd, 1H, J=6Hz, 15Hz), 3.74 (s, 3H), 3.83 (m, 1H), 4.86 (dd, 1H, J=5Hz,9Hz), 5.50 (dd, 1H, J=6Hz, 9Hz), 6.96 (s, 1H), 7.02 (ddd, 1H, J=1Hz, 7Hz, 8Hz), 7.15 (ddd, 1H, J=1Hz, 7Hz, 8Hz), 7.30 (d, 1H, J=7Hz), 7.57 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 569 $(M+H)^+$, 586 $(M+H+NH_3)^+$. Anal calcd for $C_{30}H_{40}N_5O_5S \cdot 0.51$ TFA: C, 59.44; H, 6.51; N, 8.94. Found: C, 59.50; H, 6.82; N, 8.54.

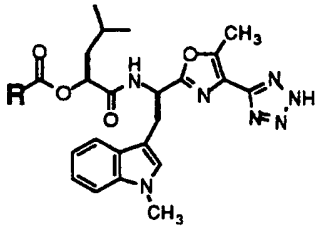
Example 50

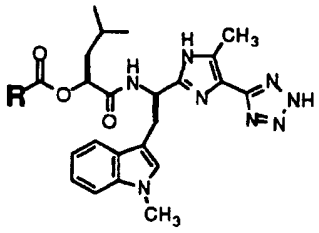
Using methods described in the above examples, compounds comprising a parent structure selected from those disclosed in Table 1A and an R substituent selected from those disclosed in Table 1B can be prepared.

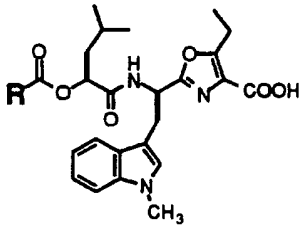
TABLE 1A

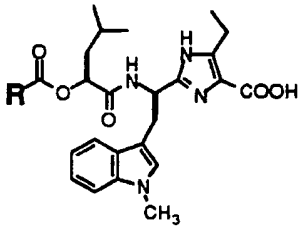
1 

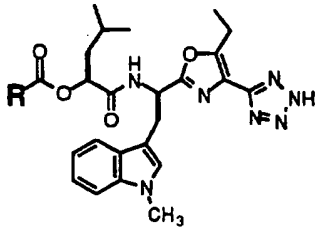
2 

3 

4 

5 

6 

7 

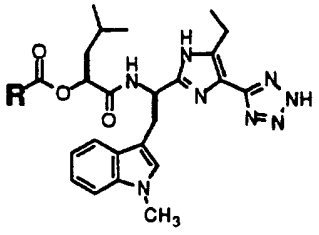
8 

TABLE 1B

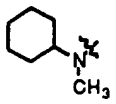
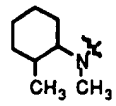
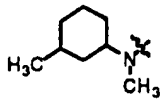
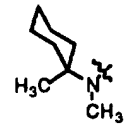
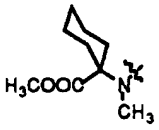
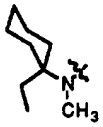
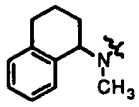
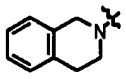
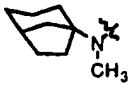
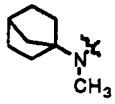
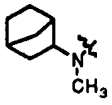
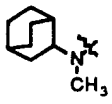
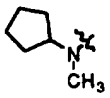
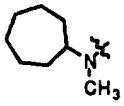
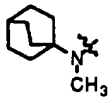
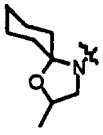
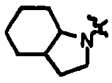
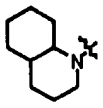
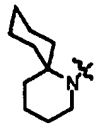
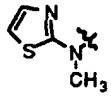
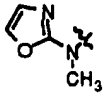
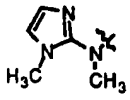
R		R		R	
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	

TABLE 1B (cont'd)

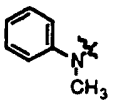
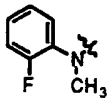
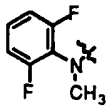
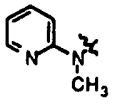
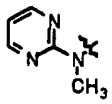
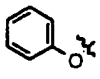
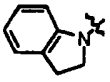
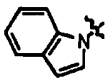
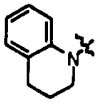
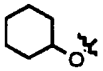
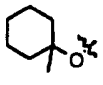
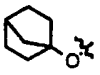
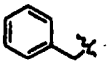
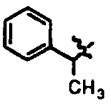
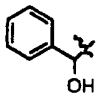
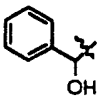
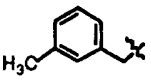
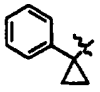
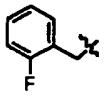
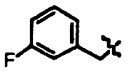
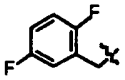
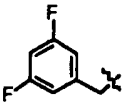
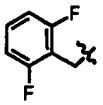
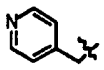
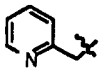
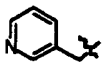
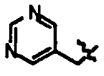
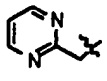
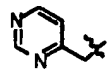
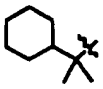
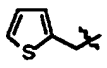
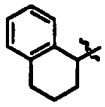
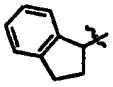
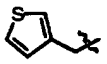
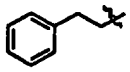
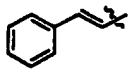
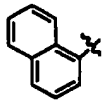
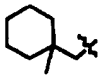
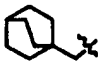
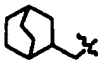
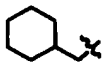
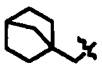
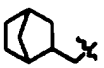
	R		R		R
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	

TABLE 1B (cont'd)

	R		R		R
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	

As an indication that the compounds described herein act through binding to endothelin receptors, the compounds have been evaluated for their ability to bind to the endothelin receptor.

Binding Assay

ET_A Receptor

Preparation of membranes from MMQ cells:

MMQ [MacLeod/MacQueen/Login cell line (prolactin secreting rat pituitary cells which are known to contain ET_A receptors)] cells from 150 ml culture flasks were collected by centrifugation (1000xg for 10 min) and then homogenized in 25 ml of 10 mM Hepes (pH 7.4) containing 0.25 M sucrose and protease inhibitors [3 mM EDTA , 0.1 mM PMSF, and 5 µg/ml Pepstatin A] by a micro ultrasonic cell disruptor (Kontes). The mixture was centrifuged at 1000xg for 10 min. The supernatant was collected and centrifuged at 60,000xg for 60 min. The precipitate was resuspended in 20 mM Tris, pH 7.4 containing the above protease inhibitors and centrifuged again. The final pellet was resuspended in 20 mM Tris, pH 7.4 containing protease inhibitors and stored at -80 °C until used. Protein content was determined by the Bio-Rad dye-binding protein assay.

[^{125}I]ET-1 binding to membranes:

Binding assays were performed in 96-well microtiter plates pretreated with 0.1% BSA. Membranes prepared from cells were diluted ~100 fold in Buffer B (20 mM Tris, 100 mM NaCl, 10 mM $MgCl_2$, pH 7.4, with 0.2% BSA, 0.1 mM PMSF, 5 µg/ml Pepstatin A, 0.025% bacitracin, and 3 mM EDTA) to a final concentration of 0.2 mg/mL of protein. In competition studies, membranes (0.02 mg) were incubated with 0.1 nM of [^{125}I]ET-1 in Buffer B (final volume: 0.2 mL) in the presence of increasing concentrations of unlabeled ET-1, BQ123, or FR139317 (reference compounds) or other tested compounds for 4 hours at 25 °C. After incubation, unbound ligands were separated from bound ligands by a vacuum filtration method using glass-fiber filter strips in PHD cell harvesters (Cambridge Technology, Inc., MA), followed by washing the filter strips with saline (1 mL) for three times. Nonspecific binding was determined in the presence of 1 µM ET-1. The data are shown in Table 2. The per cent

inhibition at a concentration of 1 μM is shown. The data show that the compounds of the invention bind to the endothelin receptor.

Table 2

Binding Data

Ex. No.	% Inhibition at 1 μM	Ex. No.	% Inhibition at 1 μM
1	96.4	26	93.9
2	93.6	27	92.5
3	94.2	28	90.6
4	88.4	29	85.7
5	93.4	30	81.7
6	94.9	31	87.5
7	24.5	32	92.5
8	95.1	33	40.9
9	94.9	35	80.1
10	97.7	36	89.3
11	74.8	37	92.6
12	85.8	38	85.6
13	21.2	39	98.2
14	81.2	40	98.9
15	80.0	41	79.3
16	94.5	42	87.1
17	76.8	43	65.6
18	95.6	44	82.4
19	95.2	45	88.6
20	96.3	46	91.5
23	37.7	47	92.0
24	91	48	96.4
25	97.1	49	68.3

As further demonstration of the efficacy of the described compounds as functional antagonists of endothelin, the ability of the described compounds to inhibit ET-1-induced phosphatidylinositol hydrolysis was measured.

Determination of Phosphatidylinositol (PI) Hydrolysis

MMQ cells (0.4 x 106 cells/mL) were labeled with 10 μCi/mL of [^{3}H]myo-inositol in RPMI for 16 hours. The cells were washed with PBS, then incubated with Buffer A containing protease inhibitors and 10 mM LiCl for 60 minutes. The cells were then incubated with test compounds for 5 minutes, and then challenged with 1 nM ET-1. ET-1 challenge was terminated by the addition of 1.5 mL of 1:2 (v/v) chloroform-methanol. Total inositol phosphates were extracted after adding chloroform and water to give final proportions of 1:1:0.9 (v/v/v) chloroform-methanol-water of as described by Berridge (Biochem. J. 206 587-595 (1982)). The upper aqueous phase (1 mL) was retained and a small portion (100 μL) was counted. The rest of the aqueous sample was analyzed by batch chromatography using anion-exchange resin AG1-X8 (Bio-Rad). The IC_{50} is the concentration of test compound required to inhibit the ET-induced increase in PI turnover by 50%. The data are shown in Table 3. The results of the above study clearly indicate that the compounds act as functional ET antagonists.

Table 3

Phosphatidylinositol Hydrolysis

Example	IC_{50} nM
1	10.5
3	1.5
4	1.2
5	6.9
6	5.6
18	25
19	37
25	4.2

As further demonstration of the efficacy of the described compounds as functional antagonists of endothelin, the ability of the described compounds to inhibit ET-1-induced constriction of vascular tissues was measured.

Functional Assay: Agonist-Induced Vasoconstriction in Isolated Tissues

Male Sprague-Dawley rats (350-500 g) were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The thoracic aorta was quickly removed and placed in a Krebs-Henseleit (KH) buffer gassed with 95/5 O_2/CO_2 to maintain pH at 7.4. Aortas were cleared of extraneous tissue and segmented into 4-5 mm wide rings which were then suspended in 2 mL jacketed tissue baths maintained at 37 °C. The tissue baths had been siliconized to prevent adsorption of peptides to glass. Vessels were attached via gold chain to an isometric force transducer linked with a physiograph for monitoring tension changes. Baseline tension was set at 2.0 g (aorta) or 0.5 g (pulmonary artery) and the tissues were allowed to equilibrate for 2.5 hours. During this period, the tissues were washed every 5 minutes with fresh KH and the tension continually adjusted to baseline. Thirty minutes into the equilibration period, tissues were maximally constricted with norepinephrine (NE, 1 μM) followed by

a challenge with acetylcholine (ACh, 3 μM). A positive relaxant response to ACh confirmed the presence of vessel endothelium. NE and ACh were then completely washed out and the tissues were allowed to return to baseline. Baseline tension was readjusted if necessary prior to any subsequent manipulations.

Constrictor Dose-Response Curves (DRCs):

ET-1 DRCs, 1E-11 to 1E-6 M, were performed in rat aorta (ETa) to establish agonist-receptor potencies in those tissues. Upon completion of the DRCs, maximal constrictor efficacy was compared with constriction by K^+ depolarization (55 mM).

Antagonist Effects on Constrictor Responses:

Antagonists tested were equilibrated 15 minutes prior to the onset of the ET-1 DRCs. Concentrations of antagonist across experimental sets were in half log increasing doses with a total of 5 different concentrations examined for each compound tested. ET-1 vehicle (control) curves were performed along side antagonist-treated curves.

Drug Potency Determination and Analysis:

Tissues in each aorta subset were from the same animal and were treated with one of the concentrations in the antagonist test range - the data was thus paired for analysis. Agonist-induced tensions from control and antagonist-treated curves were calculated and normalized against maximal contraction in those curves and the effective concentration of agonist causing 50% maximum constriction (EC_{50}) was calculated (Allfit), providing a comparative index of antagonism.

The results from one compound are shown in Table 4.

Table 4

Example	Dose	EC_{50} nM
Control	No drug	6
6	1 μM	27
6	10 μM	180

The data shows that in the presence of no drug, it takes 6 nM endothelin-1 to cause 50% of the maximum constriction of the tissue rings. In the presence of 1 μM of the product of Example 6, it takes a greater amount of endothelin-1 (the EC_{50} for endothelin-1 is shifted from 6 nM to 27 nM) to cause 50% maximal constriction. In the presence of 10 μM of the product of Example 6, it takes an even greater amount of endothelin-1 (the EC_{50} for endothelin-1 is shifted from 6 nM to 180 nM) to cause 50% maximal constriction. The results indicate that the product of Example 6 is an endothelin antagonist.

The ability of the compounds of the invention to lower blood pressure can be demonstrated according to the methods described in Matsumura, et al., Eur. J. Pharmacol. 185 103 (1990) and Takata, et al., Clin. Exp. Pharmacol. Physiol. 10 131 (1983).

The ability of the compounds of the invention to treat congestive heart failure can be demonstrated according to the method described in Margulies, et al., Circulation 82 2226 (1990).

The ability of the compounds of the invention to treat myocardial ischemia can be demonstrated according to the method described in Watanabe, et al., Circ. Res. 69 370 (1991).

The ability of the compounds of the invention to treat coronary angina can be demonstrated according to the method described in Heistad, et al., Circ. Res. 54 711 (1984).

The ability of the compounds of the invention to treat cerebral vasospasm can be demonstrated according to the methods described in Nakagomi, et al., J. Neurosurg. 66 915 (1987) or Matsumura, et al., Life Sci. 49 841-848 (1991).

The ability of the compounds of the invention to treat cerebral ischemia can be demonstrated according to the method described in Hara et al., Eur. J. Pharmacol. 197: 75-82, (1991).

The ability of the compounds of the invention to treat acute renal failure can be demonstrated according to the method described in Kon, et al., J. Clin. Invest. 83 1762 (1989).

The ability of the compounds of the invention to treat chronic renal failure can be demonstrated according to the method described in Benigni, et al., Kidney Int. 44 440-444 (1993).

The ability of the compounds of the invention to treat gastric ulceration can be demonstrated according to the method described in Wallace, et al., Am. J. Physiol. 256 G661 (1989).

The ability of the compounds of the invention to treat cyclosporin-induced nephrotoxicity can be demonstrated according to the method described in Kon, et al., Kidney Int. 37 1487 (1990).

The ability of the compounds of the invention to treat endotoxin-induced toxicity (shock) can be demonstrated according to the method described in Takahashi, et al., Clinical Sci. 79 619 (1990).

The ability of the compounds of the invention to treat asthma can be demonstrated according to the method described in Potvin and Varma, Can. J. Physiol. and Pharmacol. 67 1213 (1989).

The ability of the compounds of the invention to treat transplant-induced atherosclerosis can be demonstrated according to the method described in Foegh, et al., Atherosclerosis 78 229-236 (1989).

The ability of the compounds of the invention to treat atherosclerosis can be demonstrated according to the methods described in Bobik, et al., Am. J. Physiol. 258 C408 (1990) and/or Chobanian, et al., Hypertension 15 327 (1990).

The ability of the compounds of the invention to treat LPL-related lipoprotein disorders can be demonstrated according to the method described in Ishida, et al., Biochem. Pharmacol. 44 1431-1436 (1992).

The ability of the compounds of the invention to treat pulmonary hypertension can be demonstrated according to the methods described in Miyauchi, et al., Circ. Res. 73 887 (1993).

The ability of the compounds of the invention to treat cardiac hypertrophy can be demonstrated according to the methods described in Ito, et al., Circulation 89 2198 (1994).

The ability of the compounds of the invention to treat neointimal formation (restenosis) can be demonstrated according to the methods described in Douglas, et al., Circ. Res. 75 190 (1994).

The ability of the compounds of the invention to treat proliferative diseases can be demonstrated according to the methods described in Bunchman ET and CA Brookshire, Transplantation Proceed. 23 967-968 (1991); Yamagishi, et al., Biochem. Biophys. Res. Comm. 191 840-846 (1993); and Shichiri, et al., J. Clin. Invest. 87 1867-1871 (1991). Proliferative diseases include smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels.

The ability of the compounds of the invention to treat acute or chronic pulmonary hypertension can be demonstrated according to the method described in Bonvallet et al., Am. J. Physiol. 266 H1327 (1994). Pulmonary hypertension can be associated with congestive heart failure, mitral valve stenosis, emphysema, lung fibrosis, chronic obstructive pulmonary disease (COPD), acute repiratory distress syndrome (ARDS), altitude sickness, chemical exposure, or may be idiopathic.

The ability of the compounds of the invention to treat plaletet aggregation, and thrombosis, can be demonstrated according to the method described in McMurdo et al. Eu. J. Pharmacol. 259 51 (1994).

The ability of the compounds of the invention to treat cancers can be demonstrated according to the method described in Shichiri, et al., J. Clin. Invest. 87 1867 (1991).

The ability of the compounds of the invention to treat IL-2 (and other cytokine) mediated cardiotoxicity and vascular permeability disorders can be demonstrated according to the method described in Klemm et al., Proc. Nat. Acad. Sci. 92 2691 (1995).

The ability of the compounds of the invention to treat nociception can be demonstrated according to the method described in Yamamoto et al., J. Pharmacol. Exp. Therap. 271 156 (1994).

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate,

digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful for antagonizing endothelin in a human or other mammal. In addition, the compounds of the present invention are useful (in a human or other mammal) for the treatment of hypertension, acute or chronic pulmonary hypertension, Raynaud's disease,

congestive heart failure, myocardial ischemia, reperfusion injury, coronary angina, cerebral ischemia, cerebral vasospasm, chronic or acute renal failure, pre-eclampsia (pregnancy-induced hypertension), non-steroidal antiinflammatory drug induced gastric ulceration, immunosuppressant (for example, cyclosporin or FK 506) induced nephrotoxicity, endotoxin-induced toxicity, asthma, fibrotic or proliferative diseases, including smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, bladder dysfunction (for example, incontinence), cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels, IL-2 (and other cytokine) mediated cardiotoxicity and vascular permeability disorders, LPL-related lipoprotein disorders, cancers, nociception, plaletet aggregation, and thrombosis, transplantation-induced atherosclerosis or atherosclerosis in general.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more usually 0.1 to 100 mg/kg for oral administration or 0.01 to 10 mg/kg for parenteral administration. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or

multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capabale of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more cardiovascular agents independently selected from diuretics, adrenergic blocking agents, vasodilators, calcium channel blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, potassium channel activators and other cardiovascular agents.

Representative diuretics include hydrochlorothiazide, chlorothiazide, acetazolamide, amiloride, bumetanide, benzthiazide, ethacrynic acid, furosemide, indacrinone, metolazone, spironolactone, triamterene, chlorthalidone and the like or a pharmaceutically acceptable salt thereof.

Representative adrenergic blocking agents include phentolamine, phenoxybenzamine, prazosin, terazosin, tolazine, atenolol, metoprolol, nadolol, propranolol, timolol, carteolol and the like or a pharmaceutically acceptable salt thereof.

Representative vasodilators include hydralazine, minoxidil, diazoxide, nitroprusside and the like or a pharmaceutically acceptable salt thereof.

Representative calcium channel blockers include amrinone, bencyclane, diltiazem, fendiline, flunarizine, nicardipine, nimodipine, perhexilene, verapamil, gallopamil, nifedipine and the like or a pharmaceutically acceptable salt thereof.

Representative renin inhibitors include enalkiren, RO 42-5892, PD-134672 and the like or a pharmaceutically acceptable salt thereof.

Representative angiotensin II antagonists include DUP 753 and the like.

Representative ACE inhibitors include captopril, enalapril, lisinopril and the like or a pharmaceutically acceptable salt thereof.

Representative potassium channel activators include pinacidil and the like or a pharmaceutically acceptable salt thereof.

Other representative cardiovascular agents include sympatholytic agents such as methyldopa, clonidine, guanabenz, reserpine and the like or a pharmaceutically acceptable salt thereof.

The compounds of the invention and the cardiovascular agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents.

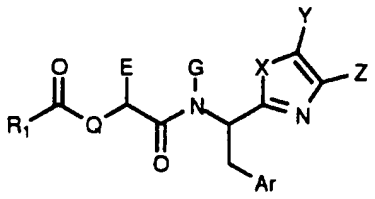
When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, processes, compositions and methods. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

CLAIMS

What is claimed is:

1. A compound of the formula:



wherein

X is -N(R_2)-, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;

Q is -O- or -CR_3R_4- wherein R_3 and R_4 are independently selected from hydrogen, loweralkyl, cycloalkyl and cycloalkylalkyl;

R_1 is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, arylalkenyl, aryl, alkoxy, arylalkoxy, cycloalkoxy, cycloalkylalkoxy, hydroxyarylalkyl, aryloxy, alkylamino, (cycloalkyl)amino, arylamino, (cycloalkylalkyl)amino, (arylalkyl)amino, dialkylamino, diarylamino, (alkyl)(cycloalkyl)amino, (alkyl)(aryl)amino, (alkyl)(cycloalkylalkyl)amino, (alkyl)(arylalkyl)amino, heterocyclic, (heterocyclic)alkyl, (heterocyclic)amino, (heterocyclic)(alkyl)amino, (heterocyclicalkyl)amino, (heterocyclicalkyl)(alkyl)amino, spirocarbocyclic or spiroheterocyclic;

E is loweralkyl optionally substituted with one, two or three substituents independently selected from cyano, halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy and azido;

G is hydrogen or loweralkyl;

Ar is bicyclic aryl, bicyclic heteroaryl or aryl;

Y is selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl; and

(7) arylalkyl; and

Z is selected from the group consisting of

(1) -C(O)-W wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) -V wherein V is

(a) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or aryl,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

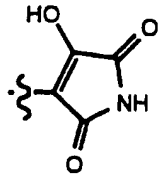
(h) tetrazolyl,

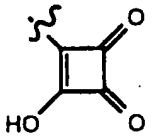
(i) hydroxy,

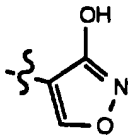
(j) alkoxy,

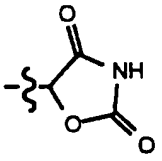
(k) sulfonamido,

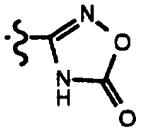
(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is defined as above,

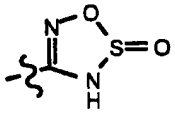
(m)  ,

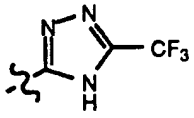
(n)  ,

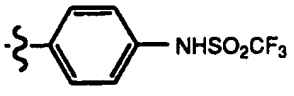
(o)  ,

(p)  ,

(q)  ,

(r)  ,

(s)  , or

(t)  ; and

(3) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl;

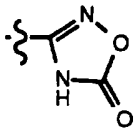
or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein

Z is

(1) -C(O)-W wherein W is -OR_{10}, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) -(tetrazolyl),



(3) or

(4) -$NHS(O)_2R_6$ wherein R_6 is loweralkyl, haloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

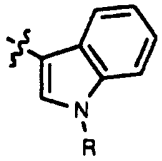
3. A compound according to Claim 1 wherein

R_1 is loweralkyl, (alkyl)(cycloalkyl)amino, cycloalkoxy, arylamino, (alkyl)(aryl)amino, diarylamino, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkoxy, (cycloalkylalkyl)amino, (cycloalkyl)amino, alkoxy, (arylalkyl)amino, dialkylamino, spiroheterocyclic or heterocyclic;

Q is -O- or -$CH(R_4)$- wherein R_4 is hydrogen or loweralkyl;

E is isobutyl;

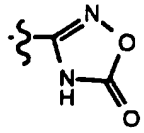
G is hydrogen;

Ar is  wherein R is hydrogen, loweralkyl or alkanoyl;

Y is hydrogen, arylalkyl, haloalkyl, loweralkyl, aryl or cycloalkyl;

Z is (1) -CO-W, wherein W is -OR_{10} wherein R_{10} is hydrogen or a carboxy protecting group,

(2) -(tetrazolyl),



(3) or

(4) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl, haloalkyl or aryl;

and

X is $-N(R_2)-$ or -O- wherein R_2 is hydrogen or loweralkyl;

or a pharmaceutically acceptable salt thereof.

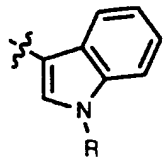
4. A compound according to Claim 1 wherein

R_1 is (cycloalkyl)amino, arylamino, aryl, arylalkyl, spiroheterocyclic, heterocyclic, (alkyl)(aryl)amino, cycloalkoxy, cycloalkylalkyl or (alkyl)(cycloalkyl)amino;

Q is -O- or $-CH_2-$;

E is isobutyl;

G is hydrogen;



Ar is wherein R is loweralkyl;

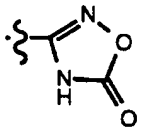
X is -NH- or -O-,

Y is loweralkyl; and

Z is

(1) $-CO_2H$,

(2) -(tetrazolyl),

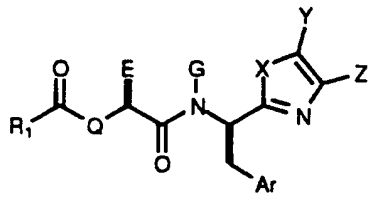


(3) or

(4) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl or aryl;

or a pharmaceutically acceptable salt thereof.

5. A compound of the formula:



X is -N(R_2)-, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;

Q is -O- or -CR_3R_4- wherein R_3 and R_4 are independently selected from hydrogen, loweralkyl, cycloalkyl and cycloalkylalkyl;

R_1 is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, arylalkenyl, aryl, alkoxy, arylalkoxy, cycloalkoxy, cycloalkylalkoxy, hydroxyarylalkyl, aryloxy, alkylamino, (cycloalkyl)amino, arylamino, (cycloalkylalkyl)amino, (arylalkyl)amino, dialkylamino, diarylamino, (alkyl)(cycloalkyl)amino, (alkyl)(aryl)amino, (alkyl)(cycloalkylalkyl)amino, (alkyl)(arylalkyl)amino, heterocyclic, (heterocyclic)alkyl, (heterocyclic)amino, (heterocyclic)(alkyl)amino, (heterocyclicalkyl)amino, (heterocyclicalkyl)(alkyl)amino, spirocarbocyclic or spiroheterocyclic;

E is loweralkyl optionally substituted with one, two or three substituents independently selected from cyano, halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy and azido;

G is hydrogen or loweralkyl;

Ar is bicyclic aryl, bicyclic heteroaryl or aryl;

Y is selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy,

amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl; and

(7) arylalkyl; and

Z is selected from the group consisting of

(1) -C(O)-W wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) -V wherein V is

(a) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or aryl,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

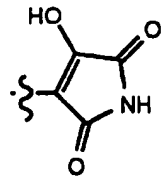
(h) tetrazolyl,

(i) hydroxy,

(j) alkoxy,

(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is defined as above,

(m) 

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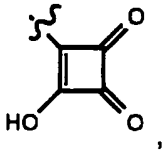
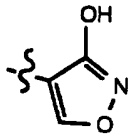
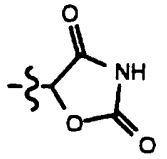
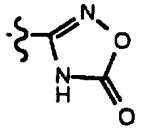
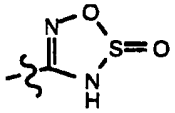
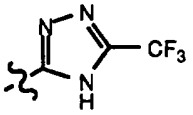
(n)  ,

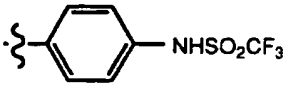
(o)  ,

(p)  ,

(q)  ,

(r)  ,

(s)  , or

(t)  ; and

(3) -NHS(O)$_2$R$_6$ wherein R$_6$ is loweralkyl or haloalkyl;

or a pharmaceutically acceptable salt thereof.

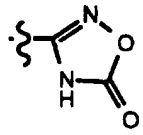
6. A compound according to Claim 5 wherein

Z is

(1) -C(O)-W wherein W is -OR$_{10}$, wherein R$_{10}$ is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino,

N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) -(tetrazolyl),



(3) or

(4) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl, haloalkyl or aryl;

or a pharmaceutically acceptable salt thereof.

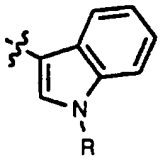
7. A compound according to Claim 5 wherein

R_1 is loweralkyl, (alkyl)(cycloalkyl)amino, cycloalkoxy, arylamino, (alkyl)(aryl)amino, diarylamino, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkoxy, (cycloalkylalkyl)amino, (cycloalkyl)amino, alkoxy, (arylalkyl)amino, dialkylamino, spiroheterocyclic or heterocyclic;

Q is -O- or $-CH(R_4)-$ wherein R_4 is hydrogen or loweralkyl;

E is isobutyl;

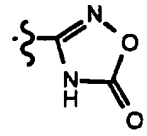
G is hydrogen;

Ar is  wherein R is hydrogen, loweralkyl or alkanoyl;

Y is hydrogen, arylalkyl, haloalkyl, loweralkyl, aryl or cycloalkyl;

Z is (1) -CO-W, wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group,

(2) -(tetrazolyl),

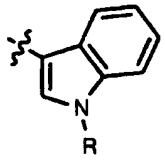
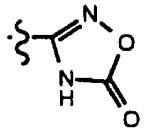


(3) or

(4) $-NHS(O)_2R_6$ wherein R_6 is loweralkyl, haloalkyl or aryl;

and

X is -N(R_2)- or -O- wherein R_2 is hydrogen or loweralkyl;
or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 5 wherein
R_1 is (cycloalkyl)amino, arylamino, aryl, arylalkyl, spiroheterocyclic, heterocyclic, (alkyl)(aryl)amino, cycloalkoxy, cycloalkylalkyl or (alkyl)(cycloalkyl)amino;
Q is -O- or -CH_2-;
E is isobutyl;
G is hydrogen;
Ar is  wherein R is loweralkyl;
X is -NH- or -O-,
Y is loweralkyl; and
Z is
(1) -CO_2H,
(2) -(tetrazolyl),
(3)  or
(4) -NHS(O)$_2R_6$ wherein R_6 is loweralkyl or aryl;
or a pharmaceutically acceptable salt thereof.

9. A compound selected from the group consisting of:

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(2S)-(2-(Cyclohexyloxycarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Azaspiro[4.5]decane-4-carboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Methyl-N-phenylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)aminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-(2-Fluorophenyl)-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Fluoro-1-indolinylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(N-Cyclohexyl-N-methylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2R)-(2-(1-Indolinylcarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(1-Naphthylcarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Cyclohexylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1S)-1-(N-(2S)-(2-(N-Cyclohexylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1S)-1-(N-(2R)-(2-(N-Cyclohexylaminocarbonylmethyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(Phenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(3-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(4-Fluorophenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(3-Methylphenylacetoxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-((2S)-(+)-2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2-Phenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(2,6-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;2-{(1R)-1-(N-(2S)-(2-(2,4-Difluorophenylpropionyl)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid (4-isopropylbenzenesulfonyl)carboxamide;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid (methanesulfonyl)carboxamide;

2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(4H-[1,2,4]oxadiazol-5-on-3-yl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(5-tetrazolyl)oxazole;

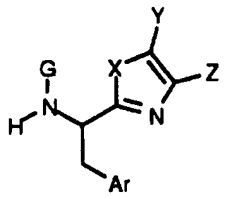
2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-4-(5-tetrazolyl)oxazole;

2-{(1R)-1-(N-(2S)-(2-(N-Cyclohexyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid; and

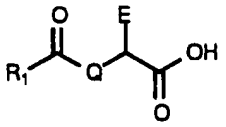
2-{(1R)-1-(N-(2S)-(2-(N-Phenyl-N-methylaminocarboxy)-isovaleryl)-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

10. A process for preparing the compound of Claim 1 comprising reacting a compound of the formula:



wherein Ar, G, X, Y and Z are as defined therein with a compound of the formula:



or an activated derivative thereof

wherein R_1, Q and E are as defined in Claim 1.

11. A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of the compound of Claim 1 and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of the compound of Claim 5 and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of the compound of Claim 9 and a pharmaceutically acceptable carrier.

14. A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

15. A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 5.

16. A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 9.

17. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

18. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising

administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 5.

19. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 9.

20. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with one or more cardiovascular agents.

21. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 5 in combination with one or more cardiovascular agents.

22. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 9 in combination with one or more cardiovascular agents.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/13373

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/06 C07D413/14 A61K31/41 A61K31/42 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 460 679 (BANYU PHARMA CO LTD) 11 December 1991 see claim 1	
P,A	WO,A,95 08550 (ABBOTT LAB) 30 March 1995 see claims	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 1996	07.02.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. ıational application No.

PCT/US95/13373

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-22 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/13373

Patent document cited in search report	Publication date	Patent family member(s)		Publicauon date
EP-A-0460679	11-12-91	AU-B-	632695	07-01-93
		AU-B-	7818291	12-12-91
		JP-A-	5178891	20-07-93
		US-A-	5470833	28-11-95
		US-A-	5444152	22-08-95
WO-A-9508550	30-03-95	NONE		